

SCIENTIFIC DISCUSSION

This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets ¹
Manufacturer of Prequalified Product:	Micro Labs Limited Plot No: S-155 to S-159 & N1 Phase III & IV Verna Industrial Estate Verna, Goa- 403722 India
Active Pharmaceutical Ingredients (APIs):	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Codes):	Antivirals for treatment of HIV infections, combinations (emtricitabine and tenofovir disoproxil: J05AR03)
Therapeutic indication:	<p>Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is indicated for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infected adults and adolescents from 10 years of age and weighing \geq 30 kg.</p> <p>Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets may be used for pre-exposure prophylaxis in adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection.</p>

¹ Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

1. Introduction

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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.

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets may be used for pre-exposure prophylaxis in certain high-risk populations.

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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

Based on scientific principles the WHO Prequalification Team – Medicines has identified emtricitabine (up to 200 mg oral dose) as a BCS class 1 API. Emtricitabine is thus highly soluble in aqueous medium over the pH range 1.0 – 6.8.

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 Emtricitabine/ Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets, 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 inspection 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. Solubility data demonstrated that TDF is highly soluble in aqueous medium over the pH range 1.0 – 6.8.

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. 112-114⁰C) and a high melting form (m.p. 114-118⁰C). The high melting form, controlled by XRPD and melting point, is consistently produced.

The specifications for TDF include tests for description, solubility, identification (IR, HPLC), polymorphic form (XRPD), clarity of solution, water content, heavy metals, residue on ignition, melting point (DSC), related compounds (HPLC), enantiomeric impurity ($\leq 0.40\%$; chiral HPLC), assay (HPLC), fumaric acid content, residual solvents and particle size. The specifications also control the mutagenic 9-propenyladenine, which is a synthesis related substance, at ≤ 5 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int. 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 packaging.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, pregelatinized starch and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hypromellose, lactose monohydrate, titanium dioxide, triacetin and FD&C Blue # 2 / Indigo carmine aluminum lake. TSE / BSE free attestations have been provided for 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, film coated tablet, debossed with 'T' on one side and '45' on the other side. The tablets are packaged in Alu-Alu blister cards or in HDPE bottles, with white polypropylene child resistant cap. The bottle pack also includes a canister containing silica gel desiccant to protect the tablets from moisture.

The objective of the development programme was to obtain a stable, immediate-release FDC tablet that is bioequivalent to the WHO comparator product Truvada®. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information on the qualitative composition of the comparator product and compatibility with the APIs. Characterization of the comparator product identified a quality target product profile, including multipoint dissolution in BCS related media.

Wet granulation was selected as a method of manufacture of the core tablets due to poor flow properties and compressibility of both APIs. Trial formulas were developed and optimized as per QTPP. Satisfactory in-process controls have been established.

Specifications

The finished product specifications include tests for description, identification (HPLC, TLC), average weight, tablet dimensions, disintegration time, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents (GC) and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed 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 2012 according to internationally accepted guidelines.

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of Emtricitabine and Tenofovir disoproxil fumarate tablets 200/300 mg of Micro Labs Limited, India with Truvada® (emtricitabine and tenofovir disoproxil fumarate) tablets of Gilead

Sciences Inc. Foster City, CA 94404 in normal, healthy, adult, human subjects under fasting condition (study no. ARL/12/112).

The objective of the study was to compare the bioavailability of the stated Emtricitabine/ Tenofovir disoproxil fumarate 200/300 mg FDC tablet manufactured by/for Micro Labs Limited, India (test drug) with 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 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 200/300 mg (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. EDAG002.
- Treatment R: Reference – 1 tablet Truvada® (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. DBNN.

An 11 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 21 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 validated LC-MS/MS methods. The limit of quantification was stated to be about 35 ng/ml for emtricitabine and 10 ng/ml for tenofovir.

The study was performed with 46 participants; data generated from a total of 42 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVA log)
t _{max} (h)	2.04 ± 0.83	1.80 ± 0.61	-	-
C _{max} (ng/ml)	2268 ± 638 (2189)	2245 ± 519 (2190)	100.0	95.5 – 104.6
AUC _{0-t} (ng.h/ml)	12702 ± 2537 (12452)	12593 ± 2355 (12377)	100.6	97.4 – 103.9
AUC _{0-inf} (ng.h/ml)	13115 ± 2529 (12877)	12978 ± 2341 (12772)	100.8	97.9 – 103.8

* 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)
t _{max} (h)	1.41 ± 0.67	1.28 ± 0.51	-	-
C _{max} (ng/ml)	356 ± 103 (341)	350 ± 93 (337)	101.2	95.3 – 107.5
AUC _{0-72h} (ng.h/ml)	2618 ± 852 (2492)	2681 ± 851 (2555)	97.5	92.7 – 102.6

* 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 test FDC tablet Emtricitabine/Tenofovir disoproxil fumarate 200mg/300 mg 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

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Truvada® (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) 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 Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets is used in accordance with the SmPC.

Bioequivalence

Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets has shown to be bioequivalent with Truvada® 200 mg/300 mg tablets (Gilead Sciences Inc., USA).

Efficacy and Safety

Regarding clinical efficacy and safety, Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets 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 has advised that the quality, efficacy and safety of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets allow inclusion of Emtricitabine/Tenofovir Disoproxil Fumarate 200 mg/300 mg Tablets, manufactured at Micro Labs Limited, Plot No: S-155 to S-159 & N1, Phase III & IV, Verna Industrial Estate, Verna, Goa - 403722, India, in the list of prequalified medicinal products.