SCIENTIFIC DISCUSSION

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

Name of the Finished Pharmaceutical Product:	[HA715 trade name][*]
Manufacturer of Prequalified Product:	Lupin Limited Plot No. 6A1, 6A2, Sector-17 Special Economic Zone MIHAN Nagpur Maharashtra 441 108 India
Active Pharmaceutical Ingredients (APIs):	Emtricitabine, tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Codes):	Antivirals for treatment of HIV infections, (J05AR03)
Therapeutic indication:	[HA715 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. [HA715 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.

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

1. Introduction

[HA715 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 over 10 years of age and weighing at least 30 kg. [HA715 trade name] may be used for pre-exposure prophylaxis in certain high-risk populations.

[HA715 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 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 according to the BCS.

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, with L-menthol as the starting material for synthesis. Emtricitabine is known to exhibit polymorphism. Form I is consistently produced.

The API specifications include tests for description, solubility, identification (IR), specific optical rotation, polymorphic identity (XPRD), loss on drying, sulphated ash, heavy metals, organic impurities (HPLC), assay (potentiomeric), residual solvents, particle size distribution , content of alkyl methane sulfonates (GC-MS; each individual ≤ 6.25 ppm) 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.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate (TDF) 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 tenofovir disoproxil fumarate, used in the manufacture of [HA715 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.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, lactose monohydrate, pregelatinized starch, croscarmellose sodium and magnesium stearate. The commercially sourced proprietary film-coating mixture contains hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, triacetin and FD & C Blue #2/Indigo carmine aluminium lake. TSE/BSE free certificates 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 .

The multisource product is a blue coloured, capsule shaped, biconvex, film-coated tablet, plain on both sides. The tablets are packaged in a white opaque, round HDPE bottle with white non-child resistant polypropylene closure with heat seal liner. The bottle also contains either a 5g silica gel desiccant sachet or a 5g molecular sieve desiccant sachet.

The objective of the formulation development was to develop a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO comparator product, Truvada® film coated tablets (emtricitabine/tenofovir disoproxil fumarate 200mg/300mg). The selection of excipients was based on the qualitative composition of the comparator product, supported by API-excipient compatibility studies. Emtricitabine and tenofovir disoproxil fumarate APIs are sensitive to moisture therefore dry granulation involving several compaction steps was selected as the manufacturing process. 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 and TLC) and colorants, water content (KF), dissolution (HPLC detection), uniformity of dosage units (by weight variation), assay (HPLC), related substances (HPLC), and microbial limits. The test methods have been satisfactorily validated.

Stability testing
Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. Slight degradation was observed for TDF, 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. The product should be protected from light and excursions above 30°C should be avoided.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bioequivalence

The following bioequivalence study has been performed in 2017 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 mg and 300 mg of Lupin Limited, India with Truvada® (emtricitabine and tenofovir disoproxil fumarate) 200mg/300mg tablets of Gilead Sciences Inc., Foster City, CA 94404, in normal, healthy, adult, male and female human subjects under fasting conditions (study no. ARL/17/376).

The objective of the study was to compare the bioavailability of the stated Emtricitabine/Tenofovir Disoproxil Fumarate 200mg/300mg FDC tablet manufactured by/for Lupin 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 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/300mg (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. M790907.
Treatment R:	Reference – 1 tablet Truvada® (emtricitabine 200 mg + tenofovir disoproxil fumarate 300 mg) Batch no. 003123.

A 11 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 72h 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 40 ng/ml for emtricitabine and 5 ng/ml for tenofovir.

The study was performed with 28 participants; data generated from a total of 28 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 (ANOVAlog)
t_{max} (h)[#]	1.75 ± 0.81	1.79 ± 0.89	-	-
C_{max} (ng/ml)	2225 ± 464 (2173)	2351 ± 497 (2296)	94.6	87.8 – 102.0
AUC_{0-t} (ng.h/ml)	12064 ± 1690 (11950)	12410 ± 2015 (12255)	97.5	92.6 – 102.7
AUC_{0-inf} (ng.h/ml)	12507 ± 1662	12834 ± 2073	-	-

* 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)[#]	1.24 ± 0.66	1.34 ± 0.65	-	-
C_{max} (ng/ml)	340 ± 98 (326)	350 ± 87 (339)	96.1	86.9 – 106.3
AUC_{0-t} (ng.h/ml)	2690 ± 562 (2622)	2948 ± 787 (2853)	91.9	86.7 – 97.4
AUC_{0-inf} (ng.h/ml)	2932 ± 593	3163 ± 796	-	-

* geometric mean

Conclusion

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 Truvada® (Gilead Sciences Inc.).

4. Summary of Product Safety and Efficacy

[HA715 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator products. According to the submitted data on quality and

bioavailability [HA715 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 [HA715 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA715 trade name] has shown to be bioequivalent to Truvada® 200mg/300mg tablets (Gilead Sciences Inc., USA).

Efficacy and Safety

Regarding clinical efficacy and safety [HA715 trade name] is considered effective and safe to use when the guidance and restrictions presented 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 [HA715 trade name] was acceptable for the following indication: **"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 [HA715 trade name] allow inclusion of [HA715 trade name], manufactured at Lupin Limited, Plot No. 6A1, 6A2, Sector-17, Special Economic Zone, MIHAN, Nagpur, Maharashtra, 441 108, India in the list of prequalified medicinal products.