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	[HA703 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited Unit 1, block-1, Plot No. 6A, Sector-17, Special Economic Zone, MIHAN Notified Area, Nagpur, Maharashtra-4411 08, India
Active Pharmaceutical Ingredient(s) (API)	Lamivudine/tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR12)
Therapeutic indication	[HA703 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing at least 30 kg or more. [HA703 trade name] may be used for pre-exposure prophylaxis (PrEP) as an additional prevention choice for adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection as part of combination prevention approaches.

1. Introduction

[HA703 trade name] is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing at least 30 kg or more.

[HA703 trade name] may be used for pre-exposure prophylaxis (PrEP) as an additional prevention choice for adults and adolescents (weighing at least 35 kg) at substantial risk of HIV infection as part of combination prevention approaches.

Therapy 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)

Lamivudine

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

Based on scientific principles WHO PQTm has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. The API is thus BCS highly soluble. Lamivudine API is described in the Ph. Int, Ph. Eur and USP, and is considered well-established in the WHO PQTm.

The API specifications are pharmacopoeial based and include tests for description, solubility, melting point, identification (IR and HPLC), light absorption, water content (KF), residue on ignition, related substances (HPLC), limit of lamivudine enantiomer (≤ 0.30%), assay (HPLC), residual solvents (GC), particle size distribution, bulk density, tapped density, toluene sulfonates (LC-MS/MS; each ≤ 5 ppm) , methane sulfonates (GC-MS; each ≤ 5 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 packing material.

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 [HA703 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, croscarmellose sodium, magnesium stearate, hypromellose, colloidal silicon dioxide and talc. The commercially sourced proprietary film-coating mixture contains hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide and triacetin. TSE/BSE free certificates have been provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

The multisource product is a white-coloured, capsule-shaped, biconvex, film-coated tablet, plain on both sides. The tablets are packaged in a white opaque, round HDPE bottle with white, round, fine-ribbed non-child resistant polypropylene closure with heat seal liner. The bottle also contains a 5 g silica gel 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 products, Epivir tablets (lamivudine 300 mg) and Viread tablets (tenofovir disoproxil fumarate 300 mg). The selection of excipients was based on the qualitative composition of the comparator products and supported by API-excipient compatibility studies. The manufacturing process of [HA703 trade name] involves aqueous wet granulation of the lamivudine part and compaction of the tenofovir disoproxil fumarate part followed by blending, compression and film-coating. 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, uniformity of dosage units (by mass variation), water content (KF), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30ºC/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 tenofovir disoproxil fumarate, 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 2017 according to internationally accepted guidelines.

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study comparing [HA703 trade name] of Lupin Limited, India, with individual reference products Epivir® (lamivudine) tablets 300 mg of GlaxoSmithKline, Research Triangle Park, NC 27709 and Viread® (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Intl Ltd, in normal, healthy, adult, male human subjects under fasting conditions (study no. ARL/17/048).

The objective of the study was to compare the bioavailability of [HA703 trade name] tablet manufactured by/for Lupin Limited, India (test drug) with the reference formulations Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Intl Ltd.) 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 [HA703 trade name] (lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. M790530.
Treatment R:	Reference – 1 tablet Epivir® (lamivudine 300 mg) Batch no. 5ZP1465. – 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. A258211D8

An 8 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 18 samples within 48h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for lamivudine and tenofovir were analyzed using validated LC-MS/MS method. The limit of quantification was stated to be about 80 ng/mL for lamivudine and 10 ng/mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 35 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine and tenofovir as well as statistical results are summarised in the following tables:

Lamivudine

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 (ANOVAlog)
t_{max} (h)	1.98 ± 0.87	1.62 ± 0.95	-	-
C_{max} (ng/mL)	2487 ± 815 (2344)	2478 ± 825 (2338)	100.3	92.1 – 109.2
AUC_{0-t} (ng·h/mL)	12105 ± 3405 (11507)	11560 ± 3495 (10996)	104.6	97.9 – 111.9
AUC_{0-inf} (ng·h/mL)	12651 ± 3403 (12112)	12123 ± 3478 (11608)	104.3	98.4 – 110.7

Tenofovir

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 (ANOVAlog)
t_{max} (h)	1.47 ± 075	0.93 ± 0.33	-	-
C_{max} (ng/mL)	203 ± 59 (195)	228 ± 60 (220)	88.7	81.8 – 96.1
AUC_{0-t} (ng·h/mL)	1433 ± 566 (1337)	1416 ± 521 (1332)	100.3	93.0 – 108.3
AUC_{0-inf} (ng·h/mL)	1821 ± 611 (1730)	1826 ± 547 (1752)	98.7	92.4 – 105.5

The results of the study show that preset acceptance limits of 80-125 % are met by both AUC and Cmax values regarding lamivudine and tenofovir. Accordingly, the test [HA703 trade name] tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Intl Inc.).

4. Summary of product safety and efficacy

[HA703 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, [HA703 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Intl Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA703 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 [HA703 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA703 trade name] has been shown to be bioequivalent with Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Intl Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA703 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 [HA703 trade name] was acceptable for the following indication: 'in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in patients weighing at least 30 kg or more and for pre-exposure prophylaxis in certain high-risk populations', and would allow inclusion of [HA703 trade name], manufactured at Lupin Limited, Unit 1, block-1,Plot No. 6A, Sector-17, Special Economic Zone, MIHAN Notified Area, Nagpur, Maharashtra-4411 08, India in the list of prequalified medicinal products.