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	[HA770 trade name]*
Manufacturer of Prequalified Product	Cipla Limited, Plot No A – 42 (Unit – II), MIDC, Patalganga District-Raigad, Maharashtra-410 220, India Cipla Quality Chemical Industries Limited (Cipla QCIL) Plot 1-7, 1st Ring Road, Luzira Industrial Park, P.O Box 34871, Kampala, Uganda
Active Pharmaceutical Ingredients (APIs)	Efavirenz/ Lamivudine/Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations ATC code: J05AR11
Therapeutic indication	[HA770 trade name] is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in patients weighing at least 30 kg.

1. Introduction

[HA770 trade name] is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in patients weighing at least 30 kg as detailed in the summary of product characteristics.

The 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)

Efavirenz

Data provided in the dossier show that efavirenz is of BCS low solubility across the physiological pH range, hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. Efavirenz can exist in several crystalline forms; form I, characterized X-ray powder diffraction (XRPD), is consistently produced. The acceptance criteria for PSD were set on information of the API lot related to the FPP biobatch.

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

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and UV), assay (HPLC), inorganic impurities(residue on ignition), organic impurities (HPLC), completeness of solution, water determination (coulometry), enantiomeric purity (HPLC), particle size distribution (laser diffraction), loss on drying, benzene content (GC; ≤2ppm), zinc content (ICP-MS; ≤1300ppm), specific optical rotation, polymorphic identity (XRPD) and residual solvents (GC).

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.

Lamivudine and Tenofovir disoproxil fumarate

Lamivudine 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 these APIs, used in the manufacture of [HA770 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 croscarmellose sodium, microcrystalline cellulose, yellow iron oxide, magnesium stearate, pregelatinised starch, sodium lauryl sulfate, hydroxypropyl cellulose and lactose monohydrate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, polyethylene glycol, lecithin (soya), talc, titanium dioxide and yellow iron oxide. TSE/BSE free certificate from the supplier has been provided with regard to lactose. Lactose and magnesium stearate are of bovine and vegetable origin respectively.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

Each tablet contains 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of TDF equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir.

The multisource product is a yellow coloured, oblong shaped, biconvex, film coated tablet with "T4" debossed on one side and plain on the other side. The tablets are presented in white opaque HDPE bottles with either one or three silica gel bags and closed with white polypropylene screw caps with inner wad/ induction seals.

The aim of the development was to formulate an immediate release, FDC dosage form, which is stable, and bioequivalent to the WHO comparator product Symfi Lo™ tablets (efavirenz/lamivudine/ tenofovir disoproxil fumarate 400 mg/300 mg/300 mg). The comparator product was characterized and on that basis a quality target product profile was defined, and critical quality attributes were identified. The excipients were selected based on excipients used in the comparator product and prior experience with a similar prequalified product (HA593). Wet granulation of the individual APIs was selected due to the high content and poor compressibility of efavirenz and tenofovir disoproxil fumarate. As per literature and from studies of API-excipient compatibility, it was evident that tenofovir disoproxil fumarate is incompatible with sodium lauryl sulfate (SLS), hence, this product is designed to be a bilayer tablet having the critically insoluble efavirenz with SLS in one layer and the second layer consisting of tenofovir disoproxil fumarate with lamivudine. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain coated tablets of desired characteristics. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and TLC), identification of colorants, average weight, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), degradation products (HPLC), assay (HPLC), residual solvents, polymorphic identity 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 within agreed limits. Based on the available stability data, the proposed shelf-life and storage conditions of the unopened bottles as stated in the SmPC are acceptable. The in-use storage period after first opening of the bottle is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2021 according to internationally accepted guidelines.

A randomized, single dose, open label, two-period, cross-over, oral, bioequivalence study between the test product, Efavirenz 400 mg + Lamivudine 300 mg + Tenofovir Disoproxil Fumarate 300 mg tablet (Cipla Ltd., India) and the reference product, Symfi Lo™ (efavirenz 400 mg/ lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) tablets (Mylan Specialty L.P. Morgantown, WV 26505 U.S.A) in healthy adult human subjects under fasting conditions (study no. 18-08-182).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 400mg/300mg/300mg FDC tablet manufactured by/for Cipla Ltd., India (test drug) with the reference formulation Symfi Lo™ (Mylan Specialty L.P. Morgantown) 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 Efavirenz/lamivudine/tenofovir disoproxil fumarate 400mg/300mg/300mg (efavirenz 400 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. PB00852.
Treatment R:	Reference – 1 tablet Symfi Lo™ (efavirenz 400 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. 8090821

A 35-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for efavirenz, lamivudine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 80 ng/mL for efavirenz, 20 ng/mL for lamivudine and 5 ng/mL for tenofovir.

The study was performed with 80 participants; data generated from a total of 65 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Efavirenz

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)	3.74 ± 1.32	3.54 ± 1.52	–	–
C_{max} (ng/mL)	1566 ± 512 (1491)	1477 ± 588 (1384)	107.7	100.6 – 115.3
AUC_{0-72h} (ng·h/mL)	31922 ± 8784 (30551)	31473 ± 9934 (29731)	102.8	98.2 – 107.6

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)	2.22 ± 1.08	2.16 ± 0.93	–	–
C_{max} (ng/mL)	2270 ± 602 (2185)	2310 ± 576 (2242)	97.5	91.9 – 103.4
AUC_{0-t} (ng·h/mL)	12249 ± 3144 (11832)	12011 ± 2807 (11679)	101.3	97.0 – 105.8
AUC_{0-inf} (ng·h/mL)	12511 ± 3130 (12108)	12317 ± 2818 (11992)	101.0	96.8 – 105.3

Tenofovir disoproxil fumarate

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)	1.56 ± 0.77	1.61 ± 0.77	–	–
C_{max} (ng/mL)	316 ± 77 (306)	300 ± 88 (287)	106.7	101.7 – 111.8
AUC_{0-t} (ng·h/mL)	2487 ± 736 (2380)	2406 ± 744 (2281)	104.3	100.0 – 108.9
AUC_{0-inf} (ng·h/mL)	2705 ± 752 (2604)	2623 ± 771 (2505)	104.0	100.1 – 108.0

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding efavirenz, lamivudine and tenofovir. Accordingly, the test Efavirenz/lamivudine/tenofovir disoproxil fumarate 400 mg/300 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 Symfi Lo™ (Mylan Specialty L.P. Morgantown).

4. Summary of product safety and efficacy

[HA770 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, [HA770 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Symfi Lo™ by Mylan Specialty L.P. Morgantown for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA770 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 [HA770 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA770 trade name] has been shown to be bioequivalent with Symfi Lo™ by Mylan Specialty L.P. Morgantown.

Efficacy and Safety

Regarding clinical efficacy and safety, [HA770 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 [HA770 trade name] was acceptable for the following indication: 'treatment of human immunodeficiency virus type 1 (HIV-1) infection in patients weighing at least 30 kg', and would allow inclusion of [HA770 trade name], manufactured at Cipla Ltd, Plot No A – 42 (Unit – II) MIDC Patalganga District Raigad Maharashtra 410 220 India and Cipla Quality Chemical Industries Limited (Cipla QCIL), Plot 1-7, 1st Ring Road, Luzira Industrial Park, P.O Box 34871, Kampala, Uganda, in the list of prequalified medicinal products.