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	[HA759 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited, Unit-V Survey No. 439, 440, 441 & 458, TSIIC-Formulation SEZ, Polepally Village, Jadcherla (Mandal), Mahaboob Nagar District Telangana State, 509 301, India
Active Pharmaceutical Ingredient(s) (API)	Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations, (J05AR11)
Therapeutic indication	[HA759 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in patients weighing at least 30 kg.

1. Introduction

[HA759 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in patients weighing at least 30 kg. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA759 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 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.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and UV), polymorphic form (XRPD), water content (KF), specific optical rotation,

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

residue on ignition, completeness of solution, organic impurities (HPLC), assay (HPLC), enantiomer content (chiral HPLC; ≤ 0.15%), residual solvents (GC), PSD (laser diffraction) and determination of metal impurities (ICP-MS).

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

Based on scientific principles WHO PQTm has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. Lamivudine is thus regarded highly soluble in terms of the BCS.

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, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.30%), other related compounds (HPLC), assay (HPLC), residual solvents (GC), toluene sulfonates (LC-MS; each ≤ 5 ppm), methane sulfonates (GC-MS; each ≤ 5 ppm) and PSD (laser diffraction).

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) 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. TDF is BCS high soluble.

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. 112-114^{0}C) and a high melting form (m.p. 114-118^{0}C). The high melting form, controlled by XRPD and melting point (DSC), is consistently produced.

The specifications for TDF include tests for description, solubility, identification (IR, HPLC), polymorphic identity (XRPD), clarity of solution, water content (KF), melting point, related substances (HPLC), 9-propenyladenine (HPLC; ≤ 5 ppm), enantiomeric purity (chiral HPLC; S-isomer ≤ 0.40%), assay (HPLC), fumaric acid content (HPLC), residual solvents (GC), particle size 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.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, hydroxypropyl cellulose, ferric oxide yellow, lactose monohydrate and magnesium stearate, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol/polyethylene glycol and talc. 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 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 white to off white, oval shaped, bevel edged biconvex film coated tablet debossed with 'H' on one side and 'E 66' on the other side. The tablets are presented in white opaque HDPE bottles with silica gel canisters and closed with white opaque child resistant polypropylene caps with pulp liners.

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 400/300/300mg). 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, prior experience with similar products and API-excipient compatibility data. Wet granulation of the individual APIs was selected due to the high content and poor compressibility of efavirenz and tenofovir disoproxil fumarate. Considering the physicochemical properties and stability of tenofovir disoproxil fumarate, isopropyl alcohol was used as its granulating solvent. 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 efavirenz component with SLS as 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, HPLC-PDA), average weight, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvent 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 2019 according to internationally accepted guidelines:

An open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single dose, oral bioequivalence study of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets 400mg/300mg/300mg of Hetero Labs Limited, India and SYMFI LO™ (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets 400mg/300mg/300mg of Mylan Specialty L.P. Morgantown, WV 26505 U.S.A in healthy, adult, human subjects under fasting conditions (study no. 195-18).

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 Hetero Labs. Limited, 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. EL019002.

Treatment R: Reference

– 1 tablet SYMFI LO™

(efavirenz 400 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)

Batch no. 8073202

A 31 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 30 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 efavirenz, lamivudine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 20 ng/ml for efavirenz, 10 ng/ml for lamivudine and 4.3 ng/ml for tenofovir.

The study was performed with 65 participants; data generated from a total of 63 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	2.56 ± 1.38	2.76 ± 1.37	-	-
C_{max} (ng/ml)	2032 ± 604 (1959)	2078 ± 589 (1992)	98.4	92.3 – 104.9
AUC_{0-72h} (ng.h/ml)	42260 ± 10480 (41185)	41798 ± 9611 (40754)	101.1	96.7 – 105.6

* geometric mean

Lamivudine

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)	1.62 ± 0.75	1.81 ± 0.78	-	-
C_{max} (ng/ml)	2187 ± 524 (2121)	2240 ± 560 (2167)	97.9	92.5 – 103.6
AUC_{0-t} (ng.h/ml)	11620 ± 2427 (11363)	12233 ± 2454 (11962)	95.0	90.9 – 99.3
AUC_{0-inf} (ng.h/ml)	11850 ± 2411 (11602)	12463 ± 2441 (12198)	95.1	91.1 – 99.3

* 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)	0.93 ± 0.38	1.08 ± 0.39	-	-
C_{max} (ng/ml)	324 ± 88 (313)	322 ± 93 (309)	101.0	96.3 – 106.0
AUC_{0-t} (ng.h/ml)	2428 ± 718 (2331)	2460 ± 689 (2363)	98.6	94.3 – 103.1
AUC_{0-inf} (ng.h/ml)	2633 ± 759 (2535)	2666 ± 714 (2573)	98.5	94.7 – 102.5

* 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 efavirenz, lamivudine and tenofovir. Accordingly, the test Efavirenz/lamivudine/tenofovir disoproxil fumarate 400mg/300mg/300mg FDC tablets meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the comparator formulation SYMFI LO™ (Mylan Specialty L.P. Morgantown).

4. Summary of product safety and efficacy

[HA759 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, [HA759 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product SYMFI LO™ (Mylan Specialty L.P. Morgantown) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA759 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 [HA759 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA759 trade name] has been shown to be bioequivalent with SYMFI LO™ (Mylan Specialty L.P. Morgantown).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA759 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 [HA759 trade name] was acceptable for the following indication: ' the treatment of human immunodeficiency virus-1 (HIV-1) infection in patients weighing at least 30 kg', and would allow inclusion of [HA759 trade name], manufactured at Hetero Labs Limited, Unit-V, Survey No. 439, 440, 441 & 458, TSIIC-Formulation SEZ, Polepally Village, Jadcherla (Mandal), Mahaboob Nagar District, Telangana State, 509 301, India in the list of prequalified medicinal products.