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	[HA767 trade name]*
Manufacturer of Prequalified Product	Micro Labs Limited Plot No S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa, 403 722, 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	[HA767 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in patients weighing at least 35 kg.

1. Introduction

[HA767 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in patients weighing at least 35 kg. [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA767 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 include tests for description, solubility, identification (IR and UV), water determination, residue on ignition, specific optical rotation, completeness of solution, organic impurities (HPLC), enantiomeric purity (HPLC; ≤ 0.15%), assay (HPLC), polymorphic form

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

(XRPD), residual solvents (GC), PSD (laser diffraction), determination of metal impurities (ICP-MS) and acetic acid content (HPLC).

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. 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, HPLC), light absorption, water content (KF), limit of lamivudine enantiomer (HPLC; ≤ 0.30%), residual solvents (GC), related substances (HPLC), assay (HPLC), residue on ignition, bulk density (untapped and tapped), particle size distribution, mesylates content (GC-MS; each ≤ 5 ppm) and tosilates content (LC-MS/MS; each ≤ 5 ppm).

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 of BCS high solubility.

TDF 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.

The TDF specifications include tests for description, solubility, identification of the API (IR, HPLC), polymorphic form (XRD), clarity of solution, water content (KF), melting point, residue on ignition, related substances (HPLC), enantiomeric purity (HPLC; S-isomer ≤ 0.4%), assay (HPLC), fumaric acid content (HPLC), residual solvents (GC), acetic acid content (HPLC) 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.

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, sodium chloride, magnesium stearate and lactose monohydrate. 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 600 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, capsule shaped, biconvex, film coated tablet debossed with ‘E34’ on one side and plain on the other side. The tablets are packaged in a white, opaque HDPE

bottle with polypropylene child resistant cap and a head induction foil inner seal. The bottle also contains a 2g molecular sieve canister.

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 ™ Tablets (efavirenz/lamivudine/ tenofovir disoproxil fumarate 600/300/300mg). The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes were identified. The excipients are qualitatively same as for the comparator product. Wet granulation manufacturing process was selected due to the poor flow and fluffy nature of the APIs. As the comparator product is a bilayer tablet, two separate manufacturing blends were proposed; efavirenz for the first layer and lamivudine and tenofovir disoproxil fumarate for the second layer.

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 a very low potential to contain nitrosamine impurities.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and PDA detector) and colorant, average weight, uniformity of weight, disintegration time, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), residual solvent (GC), elemental impurities, tablet dimensions (length, width and thickness) 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 indicated some degradation for TDF at accelerated and long-term conditions, 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 regarded acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2020 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 600mg/300mg/300mg of Micro Labs Limited, India and SYMFI™ (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets 600mg/300mg/300mg, manufactured by: Mylan Laboratories Limited, Hyderabad-500096, India and manufactured for: Mylan Specialty L.P. Morgantown, WV 26505 U.S.A., in healthy, adult, human subjects under fasting conditions (study no. 072-18).

The objective of the study was to compare the bioavailability of the stated Efavirenz/lamivudine/tenofovir disoproxil fumarate 600mg/300mg/300mg FDC tablets manufactured by/for Micro Labs. Limited, India (test drug) with the reference formulation SYMFI™ (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 600mg/300mg/300mg

(efavirenz 600 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. XLAG002.

Treatment R: Reference

– 1 tablet SYMFI™

(efavirenz 600 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)

Batch no. 3081695

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 33 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 25 ng/ml for efavirenz, 25 ng/ml for lamivudine and 4.1 ng/ml for tenofovir.

The study was performed with 32 participants; data generated from a total of 29 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)	2.95 ± 1.25	2.57 ± 1.41	-	-
C_{max} (ng/ml)	2182 ± 609 (2083)	2244 ± 795 (2117)	98.4	89.3 – 108.4
AUC_{0-72h} (ng.h/ml)	46340 ± 9836 (44841)	46906 ± 10348 (45484)	98.6	92.2 – 105.4

* 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)	1.90 ± 0.94	2.03 ± 0.98	-	-
C_{max} (ng/ml)	2153 ± 604 (2068)	2034 ± 642 (1932)	107.0	98.7 – 116.1
AUC_{0-t} (ng.h/ml)	12140 ± 3092 (11670)	11273 ± 2882 (10699)	109.1	101.8 – 116.9
AUC_{0-inf} (ng.h/ml)	12511 ± 3042 (12071)	11623 ± 2853 (11077)	109.0	101.9 – 116.5

* 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)	1.31 ± 0.47	1.04 ± 0.29	-	-
C_{max} (ng/ml)	284 ± 88 (263)	262 ± 80 (250)	105.2	96.3 – 114.9
AUC_{0-t} (ng.h/ml)	2320 ± 586 (2189)	2072 ± 509 (1972)	111.0	103.5 – 119.1
AUC_{0-inf} (ng.h/ml)	2485 ± 623 (2347)	2241 ± 556 (2133)	110.0	102.7 – 117.9

* geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding efavirenz, lamivudine and tenofovir. Accordingly, the test

Efavirenz/lamivudine/tenofovir disoproxil fumarate 600mg/300mg/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 SYMFITM (Mylan Specialty L.P. Morgantown).

4. Summary of product safety and efficacy

[HA767 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, [HA767 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product SYMFI™ (Mylan Specialty L.P. Morgantown) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA767 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 [HA767 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA767 trade name] has been shown to be bioequivalent with SYMFI™ (Mylan Specialty L.P. Morgantown).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA767 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 [HA767 trade name] was acceptable for the following indication: ' the treatment of human immunodeficiency virus-1 (HIV-1) infection in patients weighing at least 35 kg', and would allow inclusion of [HA767 trade name], manufactured at Micro Labs Limited , Plot No S-155 to S-159 & N1, Phase III & Phase IV, Verna Industrial Estate, Verna, Goa, 403 722, India in the list of prequalified medicinal products.