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	[HA764 trade name] *
Manufacturer of Prequalified Product	Aizant Drug Research Solutions Pvt. Ltd. Block No. B, Sy. No. 172 & 173, Apparel Park Rd., Dulapally Village, Dundigal- Gandimaisamma Mandal, Medchal-Malkhajgiri District, Hyderabad-500 100, Telangana, India.
Active Pharmaceutical Ingredient(s) (API)	Efavirenz,, lamivudine and tenofovir disoproxil fumarate (TDF)
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combination, J05AR11
Therapeutic indication	[HA764 trade name] is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in patients weighing at least 35 kg.

1. Introduction

[HA764 trade name] is a fixed dose combination of efavirenz, lamivudine and tenofovir disoproxil.

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

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 Ingredient (API)

Efavirenz, lamivudine and tenofovir disoproxil fumarate (TDF) 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 the APIs, used in the manufacture of [HA764 trade

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

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 lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate, hydroxypropyl cellulose, sodium chloride and pigment yellow 42. The commercially sourced proprietary pigment yellow which is included in the tablet formulation is supported by appropriate declarations and controlled by acceptable specifications. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol/PEG and talc. TSE / BSE free certificates have been provided for 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 coloured, capsule-shaped film-coated tablet with 'D19' debossed on one side and plain on other side. The tablet should be free from physical defects. The tablets are packaged in a white, round, opaque HDPE bottle with white, polypropylene child resistant closure with white outer shell embossed with pictorial design and clear inner shell fitted with a heat seal and pulp liner. The bottle also contains either one or two canisters filled with 2gm molecular sieve granules.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO recommended comparator product, Symfi TM (efavirenz/lamivudine/tenofovir disoproxil fumarate 600mg/ 300mg/ 300mg) tablets. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information of the qualitative composition of the comparator product, compatibility with the APIs and literature studies. A bilayer tablet containing the BCS low soluble efavirenz in one layer and the highly soluble lamivudine and TDF in the other layer was developed. Wet granulation manufacturing process was selected based on the high content and poor compressibility of the APIs. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

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 UV with PDA detector) and colorants, average weight, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), residual solvents (GC), elemental impurities 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

showed slight degradation for TDF, 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 acceptable.

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-period, two-sequence, single-dose, crossover, oral bioequivalence study of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate tablets 600 mg/ 300 mg/ 300mg of Aizant Drug Research Solutions Pvt. Ltd., India with SYMFI™ (efavirenz, lamivudine and tenofovir disoproxil fumarate) tablets 600 mg/ 300 mg/ 300mg mg of Mylan Specialty L.P, Morgantown, WV 26505 U.S.A. in normal healthy adult human subjects under fasting conditions. (study no. C18442).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600mg/300mg/300mg FDC tablet manufactured by/for Aizant Drug Research Solutions Pvt. Ltd., 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. ELFTA1903B.
Treatment R:	Reference – 1 tablet SYMFI™ (efavirenz 600 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. 3081695

A 35 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 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 7 ng/ml for efavirenz, 5 ng/ml for lamivudine and 3 ng/ml for tenofovir.

The study was performed with 62 participants; data generated from a total of 49 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)	3.31 ± 1.57	3.44 ± 1.55	-	-
C_{max} (ng/ml)	2214 ± 589 (2142)	2406 ± 697 (2310)	92.7	86.7 – 99.1
AUC_{0-72h} (ng.h/ml)	47939 ± 14941 (48176)	50076 ± 13715 (49958)	103.7	98.0 – 109.7

* 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)	1.97 ± 0.90	2.20 ± 1.02	-	-
C_{max} (ng/ml)	1988 ± 452 (1941)	2125 ± 620 (2042)	95.1	89.7 – 100.7
AUC_{0-t} (ng.h/ml)	12883 ± 2733 (12591)	13294 ± 2592 (13041)	96.6	91.9 – 101.4
AUC_{0-inf} (ng.h/ml)	13076 ± 2773 (12781)	13496 ± 2630 (13239)	96.5	91.9 – 101.4

* 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)	1.47 ± 0.74	1.38 ± 0.72	-	-
C_{max} (ng/ml)	288 ± 90 (275)	260 ± 72 (250)	109.6	102.0 – 117.9
AUC_{0-t} (ng.h/ml)	2383 ± 603 (2310)	2215 ± 492 (2154)	107.2	102.0 – 112.7
AUC_{0-inf} (ng.h/ml)	2601 ± 692 (2516)	2414 ± 545 (2348)	107.2	101.9 – 112.7

* 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 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 SYMFI™ (Mylan Specialty L.P. Morgantown).

4. Summary of product safety and efficacy

[HA764 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, [HA764 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product SYMFITM (Mylan Specialty L.P. Morgantown) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA764 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 [HA764 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA764 trade name] has been shown to be bioequivalent with SYMFITM (Mylan Specialty L.P. Morgantown).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA764 trade name] s 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 [HA764 trade name] was acceptable for the following indication: for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in patients weighing at least 35 kg, and would allow inclusion of [HA764 trade name] manufactured at Aizant Drug Research Solutions Pvt. Ltd., Block No. B, Sy. No. 172 & 173, Apparel Park Rd, Dulapally Village, Dundigal- Gandimaisamma Mandal, Medchal-Malkhajgiri District, Hyderabad-500 100, Telangana, India, in the list of prequalified medicinal products.