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	[HA727 trade name][*]
Manufacturer of Prequalified Product	Laurus Labs Limited, (Unit-II) Plot No. 19,20 & 21 Western Sector, APSEZ Atchutapuram Mandal Visakhapatnam-District-531011 Andhra Pradesh 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	[HA727 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and weighing at least 35 kg).

1. Introduction

[HA727 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents (from 10 years of age and weighing at least 35 kg). [See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA727 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, 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 SeriesNo. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [HA727 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

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

standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Based on the low aqueous solubility profile of Efavirenz API across the physiological pH range, particle size distribution (PSD) and polymorphism were considered to be critical API quality parameters for the FPP manufacturer. PSD limits and polymorphic form were set on the data obtained for the API batch used in the manufacture of the biobatch.

Other ingredients

Other ingredients used in the core tablet formulation include microcrystalline cellulose, sodium lauryl sulfate, hydroxypropyl cellulose, croscarmellose sodium, lactose anhydrous, magnesium stearate and pregelatinized starch, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol and talc. TSE/BSE free certificates from the suppliers have been provided with regard 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 awhite coloured, capsule shaped, biconvex film coated tablet debossed with ‘L65’ on one side and plain on the other side. The tablets are presented in white opaque HDPE bottles, each with a silica gel canister and closed with polypropylene child resistant closure with induction sealing wad.

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 600mg/300mg/300mg). The comparator product was characterized and on that basis a quality target product profile was defined and critical quality attributes (CQAs) were identified. The excipients were selected based on excipients used in the comparator product, prior experience with similar products and API-excipient compatibility data. Based on the very, very poor flow nature of API’s Efavirenz and Tenofovir Disoproxil Fumarate direct compression technique was considered as unacceptable process for this formulation. Wet granulation process was therefore proposed for the development of the product. Efavirenz and Tenofovir disoproxil fumarate APIs are wet granulated separately. 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 have a bilayer tablet having Efavirenz component with SLS as one layer and second layer consists of Tenofovir disoproxil fumarate with lamivudine in extra granular portion to overcome incompatibility of SLS with Tenofovir disoproxil fumarate. 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.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC, TLC) and colorant, uniformity of dosage units (by content uniformity), water content (KF), assay (HPLC), dissolution (HPLC detection), related substances (HPLC), 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 accelerated condition, though no significant change was observed and the results for all parameters at this storage condition were within agreed acceptance criteria. 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 of pack size of 90 tablets 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 2018 according to internationally accepted guidelines:

An open label, balanced, randomized, two-treatment, two-sequence, two-period, crossover, single-dose oral bioequivalence study of Efavirenz, lamivudine/ tenofovir disoproxil fumarate tablets 600 mg / 300 mg / 300 mg of Laurus Labs Limited, India compared with SYMFI™ (efavirenz, lamivudine, and tenofovir disoproxil fumarate) tablets 600 mg/300 mg/300 mg of Mylan Specialty L.P. Morgantown, WV 26505 U.S.A, in healthy, adult, human subjects under fasting conditions (study no. 18-117).

The objective of the study was to compare the bioavailability of the stated Efavirenz/lamivudine/tenofovir disoproxil fumarate 600mg/300mg/300 mg FDC tablet manufactured by/for Laurus Labs Limited, India (test drug) with the reference formulation Symfi™ (Mylan Specialty) 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/300 mg (efavirenz 600 mg +lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no.AELT 100118.
Treatment R:	Reference– 1 tablet Symfi™ (efavirenz 600 mg +lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. 3081695.

A 32 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 29 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, 20 ng/ml for lamivudine and 5 ng/ml for tenofovir.

The study was performed with 60 participants; data generated from a total of 52 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)	3.52 ± 1.19	3.21 ± 1.51	-	-
C_{max} (ng/ml)	2722 ± 888 (2585)	2534 ± 637 (2455)	105.3	98.9 – 112.2
AUC_{0-72h} (ng.h/ml)	58600 ± 14527 (56806)	57111 ± 12887 (55677)	102.0	97.3 – 107.0

* 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)[#]	2.20 ± 0.95	2.14 ± 1.03	-	-
C_{max} (ng/ml)	2038 ± 542 (1962)	2032 ± 629 (1933)	101.5	94.6 – 108.9
AUC_{0-t} (ng.h/ml)	11453 ± 2978 (11049)	11401 ± 3503 (10818)	102.1	95.8 – 108.9
AUC_{0-inf} (ng.h/ml)	11783 ± 2959 (11394)	11718 ± 3459 (11166)	102.0	96.1 – 108.4

* 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)[#]	1.45 ± 0.93	1.46 ± 0.82	-	-
C_{max} (ng/ml)	325 ± 105 (310)	296 ± 100 (281)	110.5	102.4 – 119.3
AUC_{0-t} (ng.h/ml)	2562 ± 716 (2462)	2443 ± 797 (2315)	106.4	99.3 – 113.9
AUC_{0-inf} (ng.h/ml)	2786 ± 742 (2689)	2680 ± 822 (2556)	105.2	98.8 – 111.9

* 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).

4. Summary of product safety and efficacy

[HA727 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, [HA727 trade name]is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Symfi™(Mylan Specialty) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [HA727 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA727 trade name] has been shown to be bioequivalent with Symfi™(Mylan Specialty).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA727 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 [HA727 trade name] was acceptable for the following indication: ' the treatment of human immunodeficiency virus-1 (HIV-1) infection in in adults and adolescents (from 10 years of age and weighing at least 35 kg)', and would allow inclusion of [HA727 trade name], manufactured at Laurus Labs Limited, (Unit-II) Western Sector, Atchutapuram Mandal, Visakhapatnam-District, Andhra Pradesh, India in the list of prequalified medicinal products.