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:	[HA732 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 (API):	Efavirenz/ Lamivudine/ Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations; J05AR11 Lamivudine, tenofovir disoproxil and efavirenz
Therapeutic indication:	[HA732 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents from 12 years of age and weighing at least 40 kg) with virologic suppression to HIV-1 RNA levels of less than 50 copies/ml on their current combination antiretroviral therapy for more than three months. Patients must not have experienced virological failure on any prior antiretroviral therapy

1. Introduction

[HA732 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].

[HA732 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 Ingredient (API)

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

Efavirenz, 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 the APIs, used in the manufacture of [HA732 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 microcrystalline cellulose, sodium lauryl sulfate, hydroxypropyl cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate and ferric oxide yellow, 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 regards to all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, film coated, oval, biconvex tablet debossed with 'L40' on one side and plain on the other side. The tablets are presented in a white opaque HDPE bottles. The bottles also contain a dessicant (silica gel or molecular sieve canisters) to protect the moisture sensitive tenofovir disoproxil fumarate from hydrolysis.

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^{TM} (efavirenz/lamivudine/tenofovir disoproxil fumarate 400mg/300mg/300mg) Tablets The excipients were selected based on the excipients used in the comparator product and API-excipient compatibility studies. As per literature, sodium lauryl sulfate is incompatible with tenofovir disoproxil fumarate, hence the multisource product was designed as a bilayered tablet having the efavirenz component with sodium lauryl sulfate as one layer and the other layer consisting of lamivudine/tenofovir disoproxil fumarate. Efavirenz API is very fluffy and static in nature and therefore to have close contact of this critically insoluble API with sodium lauryl sulfate for proper dissolution, the efavirenz part of the bilayered tablet is manufactured using wet granulation process whilst the lamivudine/tenofovir disoproxil fumarate part is manufactured using dry granulation process. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. 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. Slight degradation was observed for tenofovir disoproxil fumarate, though the degradation products remained within acceptable 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 periods after first opening of the bottles of pack sizes of 90 and 180 tablets are 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 and Tenofovir disoproxil fumarate tablets 400 mg/300 mg/300 mg of Laurus Labs Limited, India compared with SYMFI LO™ (efavirenz, lamivudine, and tenofovir disoproxil fumarate) tablets 400 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. 18-119).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 400mg/300mg/300 mg FDC tablet manufactured by/for Laurus Labs. Limited, India (test drug) with the reference FDC formulation SYMFI LO™ (Mylan) 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/300 mg
(efavirenz 400 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. AELT 200118.

Treatment R: Reference – 1 tablet SYMFI LO™
(efavirenz 400 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 8073202.

A 35 day wash-out period was observed between administration of test and references. 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 32 participants; data generated from a total of 27 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

	Test formulation	Reference	log-transformed parameters

Pharmacokinetic Parameter	(T) arithmetic mean ± SD (*)	(R) arithmetic mean ± SD (*)	Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)[#]	3.44 ± 1.32	3.26 ± 1.47	-	-
C_{max} (ng/mL)	1601 ± 473 (1552)	1746 ± 454 (1710)	90.8	85.3 – 96.6
AUC_{0-t} (ng.h/mL)	37785 ± 8985 (37181)	39723 ± 9337 (39182)	94.9	89.2 – 101.0

* 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)[#]	2.18 ± 1.13	1.61 ± 0.59	-	-
C_{max} (ng/mL)	2086 ± 585 (1996)	2124 ± 566 (2049)	97.4	90.4 – 105.0
AUC_{0-t} (ng.h/mL)	11766 ± 2727 (11409)	11329 ± 2991 (10869)	105.0	99.0 – 111.4
AUC_{0-inf} (ng.h/mL)	12143 ± 2726 (11793)	11656 ± 2982 (11216)	105.1	99.5 – 111.1

* 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)[#]	1.11 ± 0.44	1.14 ± 0.58	-	-
C_{max} (ng/mL)	393 ± 125 (374)	374 ± 98 (360)	103.8	92.9 – 116.0
AUC_{0-t} (ng.h/mL)	2692 ± 565 (2612)	2690 ± 704 (2591)	100.8	95.0 – 107.0
AUC_{0-inf} (ng.h/mL)	2911 ± 555 (2840)	2916 ± 701 (2826)	100.5	95.0 – 106.3

* 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 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 FDC formulation SYMFI LO™ (Mylan).

4. Summary of Product Safety and Efficacy

[HA732 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, [HA732 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product SYMFI LO™ (Mylan) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA732 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 [HA732 trade name] is used in accordance with the SmPC.

Bioequivalence
[HA732 trade name] has been shown to be bioequivalent with SYMFI LO™ Mylan Specialty L.P. Morgantown, WV 26505 U.S.A

Efficacy and Safety
Regarding clinical efficacy and safety, [HA732 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 [HA732 trade name] was acceptable for the following indication**: "the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 30 kg"** and has advised that the quality, efficacy and safety of [HA732 trade name] allow inclusion of [HA732 trade name], manufactured at Laurus Labs Limited, (Unit-II, Plot No. 19, 20 & 21,Western Sector, APSEZ, Atchutapuram Mandal, Visakhapatnam-District-531011, Andhra Pradesh, India in the list of prequalified medicinal products.