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:	[HA707 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):	Dolutegravir (as sodium)/ Lamivudine/ Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations, (J05AR27)
Therapeutic indication:	[HA707 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 30 kg.

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

1. Introduction

[HA707 trade name]is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 30 kg.

[See Part 4 Summary of Products Characteristics (SmPC), for full indications].

[HA707 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)

Dolutegravir sodium, 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 [HA707 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 mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, lactose monohydrate, pregelatinized starch, croscarmellose sodium and sodium stearyl fumarate, 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 coloured, oval shaped, biconvex film coated tablet debossed with 'LA75' on one side and plain on the other side. The tablets are presented in white HDPE bottles, each with a with 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 individual WHO comparator products Tivicay® (Dolutegravir 50 mg) Tablets, Epivir® (Lamivudine300 mg) Tablets and Viread® (Tenofovir disoproxil fumarate 300 mg) Tablets. The excipients were selected based on the excipients used in the comparator products and API-excipient compatibility studies. Due to the very poor flow characteristics of the dolutegravir sodium and tenofovir disoproxil fumarate APIs, it was not feasible to manufacture the tablets by direct compression. Dolutegravir granules and tenofovir granules were manufactured separately by wet granulation and lamivudine was added in the extra granular stage. 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,water content (KF), uniformity of dosage units (by content uniformity), dissolution

(HPLC detection), related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Specifications

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 2017 according to internationally accepted guidelines.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross-over, oral bioequivalence study of Dolutegravir, Lamivudine & Tenofovir disoproxil fumarate tablets 50 mg/300 mg/300 mg of Laurus Labs Limited, India comparing with that of Tivicay® (dolutegravir) tablets 50 mg of ViiV Healthcare, Research Triangle Park, NC 27709, Epivir® (lamivudine) tablets 300 mg of ViiV Healthcare Research Triangle Park, NC 27709 and Viread® (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc. Foster City, CA 94404 in healthy, adult, human subjects under fasting conditions (study no. 601/17).

The objective of the study was to compare the bioavailability of the stated Dolutegravir/ Lamivudine/ Tenofovir Disoproxil Fumarate 50 mg/300 mg/300 mg FDC tablet manufactured by/for Laurus Labs Limited, India (test drug) with the reference formulations Tivicay®(ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.) 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 Dolutegravir/Lamivudine/ Tenofovir Disoproxil Fumarate 50 mg/300 mg/300 mg (dolutegravir 50 mg +lamivudine 300 mg + tenofovir disoproxil fumarate300 mg) Batch no.ADLT100217.
Treatment R:	Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 7ZP0676. – 1 tablet Epivir® (lamivudine 300 mg) Batch no. 5ZP1465. – 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. 004052.

A 14 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 28 samples within 72 hour post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for dolutegravir, lamivudine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 20 ng/mL for dolutegravir, 15 ng/mL for lamivudine and 2.5 ng/mL for tenofovir.

The study was performed with 60 participants; data generated from a total of 56 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for dolutegravir, lamivudine and tenofovir as well as statistical results are summarised in the following tables:

Dolutegravir

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)#	3.0 (0.5 – 5.5)	2.84 (0.5 – 5.5)	-	-
C_{max} (ng/mL)	2827 ± 575 (2769)	2568 ± 550 (2510)	110.3	106.0 – 114.8
AUC_{0-t} (ng.h/mL)	53287 ± 16366 (50737)	50871 ± 13869 (48972)	103.6	99.4 – 108.0
AUC_{0-inf} (ng.h/mL)	56040 ± 18013 (53163)	53910 ± 15600 (51700)	102.8	98.5 – 107.3

* geometric mean; # as median (range)

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)#	1.75 (0.83 – 4.0)	1.38 (0.5 – 5.5)	-	-
C_{max} (ng/mL)	2199 ± 607 (2122)	2416 ± 646 (2324)	91.3	86.6 – 96.2
AUC_{0-t} (ng.h/mL)	13291 ± 2910 (12971)	13550 ± 2652 (13285)	97.6	94.0 – 101.5
AUC_{0-inf} (ng.h/mL)	13597 ± 2920 (13282)	13852 ± 2692 (13586)	97.8	94.2 – 101.5

* geometric mean; # as median (range)

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)#	0.75 (0.5 – 2.67)	0.83 (0.33 – 3.33)	-	-
C_{max} (ng/mL)	409 ± 96 (398)	403 ± 103 (389)	102.2	96.5 – 108.2
AUC_{0-t} (ng.h/mL)	3210 ± 687 (3143)	3189 ± 741 (3106)	101.2	97.8 – 104.7
AUC_{0-inf} (ng.h/mL)	3460 ± 769 (3383)	3432 ± 811 (3339)	101.3	97.8 – 105.0

* geometric mean; # as median (range)

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max}values regarding dolutegravir, lamivudine and tenofovir. Accordingly, the test Dolutegravir/ Lamivudine/Tenofovir Disoproxil Fumarate50 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 formulations Tivicay® (ViiVHealtcare), Epivir® (ViiVHealtcare) and Viread® (Gilead Sciences, Inc.).

4. Summary of product safety and efficacy

[HA707 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, [HA707 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO recommended comparator product Epivir®, Viread®and Tivicay® 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 [HA707 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA707 trade name] has shown to be bioequivalent with Tivicay® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA707 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [HA707 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 [HA707 trade name]allow inclusion of [HA707 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.