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	[HA549 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited (Unit-III) 22-110, I.D.A. Jeedimetla Hyderabad – 500055 Telangana 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	[HA549 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

[HA549 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].

[HA549 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, is consistently produced. The acceptance criteria for PSD were set on the information of the API lot used in the FPP biobatch.

The API specifications are pharmacopoeial based and include tests for description, solubility, identification (IR and UV), polymorphic form (XRPD), water content (KF), residue on ignition, heavy metals, completeness of solution, organic impurities (HPLC), assay (HPLC), limit of efavirenz

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

enantiomer (chiral HPLC; ≤ 0.15%), PSD, residual solvents (GC) and determination of metal impurities (ICP-MS).

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. Lamivudine is thus regarded highly soluble in terms of the BCS.

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), specific optical rotation, residue on ignition, heavy metals, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.30%), residual solvents (GC), related compounds (HPLC), assay (HPLC), particle size, methane sulfonates (GC-MS; each ≤ 5 ppm) and toluene sulfonates (UFLC-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 BCS high soluble.

TDF, (R)-9-(2-phosphonomethoxypropyl) adenine disoproxil fumarate, 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 specifications for TDF include tests for description, solubility, identification (IR, HPLC), clarity of solution, water content (KF), heavy metals, XRPD, melting point (DSC), related compounds (HPLC), enantiomeric impurity (≤ 0.40%; chiral HPLC), assay and fumaric acid content (HPLC), residual solvents (GC), particle size and microbiological examination. The mutagenic 9-propenyladenine, which is a synthesis related substance, is controlled at ≤ 5 ppm. This is in accordance with the requirement of Tenofovir disoproxil fumarate Ph.Int.

TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114ºC) and a high melting form (m.p. 114-118ºC). The high melting form, controlled by XRPD and melting point determination, is consistently produced.

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, anhydrous lactose, magnesium stearate, pregelatinized starch and sodium starch glycolate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol,

macrogol/PEG, titanium dioxide, talc and iron oxide yellow. BSE/TSE compliance declarations were provided.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow coloured, capsule shaped, bevel edged biconvex film coated tablet debossed with 'I' on one side and '127' on the other side. The tablets are packaged in an HDPE bottle with child resistant cap containing a bag filled with 2 gram silica gel desiccant.

The tablets have been developed as immediate release solid dosage forms for oral administration. The objective was to develop a fixed dose combination, bioequivalent to the individual WHO recommended comparator products, Viread® Tablets 300mg (TDF) Epivir® Tablets 300mg (lamivudine) and Sustiva® Tablets 600mg (efavirenz), taken concomitantly. Compatibility studies were conducted between the individual APIs and commonly employed excipients, and on API-APIexcipient and API-API-API-excipient mixtures. Based on these studies it was decided to avoid contact of efavirenz with lamivudine and TDF by developing a bi-layered tablet.

Direct compression was ruled out because of the poor flow properties of all the three APIs. The efavirenz layer is manufactured through aqueous granulation and the layer containing lamivudine and TDF by non-aqueous granulation. Several trials were conducted to optimize the formulation as well as the manufacturing process. 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 and TLC), average weight, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), related substances (HPLC), assay (HPLC), residual solvents (GC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 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 TDF, though within agreed limits. 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 2020 according to internationally accepted guidelines:

Study title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Efavirenz, Lamivudine and Tenofovir Disoproxil fumarate Tablets 600 mg/300 mg/300 mg of Hetero Labs Limited., India with Sustiva® (efavirenz) tablets 600 mg of Bristol-Myers Squibb Princeton, NJ 08543, USA and Epivir® (lamivudine) tablets 300 mg of GlaxoSmithKline Research Triangle Park, NC 27709 and Viread® (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc. Foster City, CA 94404 USA., in healthy, adult, human subjects under fasting conditions (study no. BEQ-1561-ETHI-2015).

The objective of the study was to compare the bioavailability of the stated Efavirenz/Lamivudine/Tenofovir Disoproxil fumarate 600 mg/300 mg/300 mg FDC tablet

manufactured for/by Hetero Labs Limited., India (test drug) with the individual reference formulations Sustiva® (Bristol-Myers Squibb Princeton), Epivir® (GlaxoSmithKline Research Triangle Park) 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 treatments in a randomized fashion:

Treatment T: Test – 1 tablet Efavirenz/Lamivudine/Tenofovir disoproxil fumarate 600 mg/300 mg/300 mg
(efavirenz 600 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. E161448

Treatment R: References
– 1 tablet Sustiva®
(efavirenz 600 mg)
Batch no. AAD9065B
– 1 tablet Epivir®
(lamivudine 300 mg)
Batch no. 5ZP1465
– 1 tablet Viread®
(tenofovir disoproxil 245 mg)
Batch no. 004054

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 samples within 72 h 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 a validated LC-MS/MS method. The limit of quantification was stated to be about 30 ng/ml for efavirenz, about 20 ng/ml for lamivudine and about 5 ng/ml for tenofovir.

The study was performed with 48 participants; data generated from a total of 44 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 table:

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)	3.21 ± 1.25	3.20 ± 1.99	-	-
C_{max} (µg/ml)	2.48 ± 0.75 (2.38)	2.55 ± 0.65 (2.46)	96.6	89.5 – 104.2
AUC_{0-72h} (µg.h/ml)	53.0 ± 14.1 (51.1)	54.7 ± 15.1 (52.6)	97.3	93.1 – 101.6

* 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)	1.83 ± 0.93	1.43 ± 0.81	-	-
C_{max} (ng/ml)	2303 ± 543 (2229)	2416 ± 728 (2316)	96.2	89.4 – 103.6
AUC_{0-t} (ng.h/ml)	11935 ± 2852 (11565)	11730 ± 2691 (11412)	101.3	95.5 – 107.5
AUC_{0-inf} (ng.h/ml)	12221 ± 2868 (11857)	12023 ± 2698 (11712)	101.2	95.6 – 107.2

* 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)	1.22 ± 0.63	1.16 ± 0.65	-	-
C_{max} (ng/ml)	320 ± 106 (302)	306 ± 112 (287)	105.2	98.6 – 112.2
AUC_{0-t} (ng.h/ml)	2631 ± 684 (2530)	2445 ± 753 (2333)	108.5	102.5 – 114.8
AUC_{0-inf} (ng.h/ml)	2846 ± 715 (2746)	2690 ± 796 (2580)	106.5	100.9 – 112.3

* geometric mean

Conclusion

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 600 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 individual references Sustiva® (Bristol-Myers Squibb Princeton), Epivir® (GlaxoSmithKline Research Triangle Park) and Viread® (Gilead Sciences, Inc.).

4. Summary of product safety and efficacy

[HA549 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required for the individual innovator products. According to the submitted data on quality and bioavailability [HA549 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the individual innovator products, Sustiva® (Bristol-Myers Squibb Company), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences Inc.) for which benefits have been proven in terms of virological and immunological 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 [HA549 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA549 trade name] has been shown to be bioequivalent with the individual innovator products, Sustiva® (Bristol-Myers Squibb Company), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA549 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 [HA549 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 [HA549 trade name], manufactured at Hetero Labs Limited (Unit-III), 22-110, I.D.A., Jeedimetla, Hyderabad – 500055, Telangana, India in the list of prequalified medicinal products.