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:	[HA699 trade name][*]
Manufacturer of Prequalified Product:	Sun Pharmaceutical Industries Limited Village Ganguwala Paonta Sahib District Sirmour Himachal Pradesh 173 025 India
Active Pharmaceutical Ingredient (API):	Dolutegravir (as sodium)/ Lamivudine/ Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of HIV infections, combinations, (J05AR)
Therapeutic indication:	[HA699 trade name] is indicated for the treatment of human immunodeficiency virus-Type 1 (HIV-1) infection in adults and adolescents weighing at least 30 kg.

1. Introduction

[HA699 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].

[HA699 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.*

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

Active pharmaceutical Ingredients (APIs)

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 [HA699 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, croscarmellose sodium, magnesium stearate, mannitol, sodium starch glycolate and povidone, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, talc, macrogol/polyethylene glycol and titanium dioxide. 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, capsule-shaped tablet, plain on both sides. The tablets are presented in white, opaque HDPE bottles, with either 3g, 5g or 10g silica gel desiccant and closed with white, opaque polypropylene screw caps.

The development strategy was to formulate an immediate release FDC dosage form, which is stable, and bioequivalent to the standalone WHO comparator products Tivicay® (Dolutegravir 50mg) Tablets, Epivir® (Lamivudine 300mg) Tablets and Viread® (Tenofovir disoproxil fumarate 300mg) Tablets. The excipients were selected based on the excipients used in the comparator products and excipient compatibility data; compatibility studies were conducted between the standalone APIs and commonly employed excipients, and on API-API-excipient and API-API-API-excipient mixtures. Tenofovir disoproxil fumarate API is highly sensitive to moisture; undergoes hydrolysis and forms degradation products, therefore compaction was selected as the manufacturing process for tenofovir disoproxil fumarate granules, wet granulation was selected as the literature-standard manufacturing process for dolutegravir granules and lamivudine was added extra granularly. 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 and IR) and colorant, uniformity of dosage units (by content uniformity), water content (KF), dissolution (HPLC detection), related substances (HPLC), assay (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 long-term storage condition, though 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 is based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of Bio-Equivalence

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

A single-dose, two-way crossover bioequivalence study of Dolutegravir, Lamivudine and Tenofovir Disoproxil Fumarate tablets 50mg/300mg/300mg in healthy adult human subjects under fasting condition (study no. DLT_50+300+300T_0415_17).

The objective of the study was to compare the bioavailability of the stated [HA699 trade name] FDC tablet manufactured by/for Sun Pharmaceuticals Industries Ltd., India (test drug) with the reference formulations Tivicay® (GlaxoSmithKline), Epivir® (GlaxoSmithKline) 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 [HA699 trade name] (dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. 2876278.

Treatment R: Reference – 1 tablet Tivicay® (dolutegravir 50 mg)
Batch no. 6ZP7471.
– 1 tablet Epivir® (lamivudine 300 mg)
Batch no. 5ZP1465.
– 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg)
Batch no. 005163.

An 11-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 26 samples within 72 hours 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 52 ng/mL for dolutegravir, 12 ng/mL for lamivudine and 5 ng/mL for tenofovir.

The study was performed with 66 participants; data generated from a total of 62 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90%CI (ANOVAlog)
t_{max} (h)	2.45 ± 1.22	2.78 ± 1.17	-	-
C_{max} (ng/mL)	2637 ± 589 (2578)	2478 ± 624 (2405)	107.2	102.6 – 112.0
AUC_{0-t} (ng.h/mL)	46324 ± 12529	46591 ± 14089	100.4	95.8 – 105.2

	(44702)	(44519)		
$AUC_{0\text{-}inf}$ (ng.h/mL)	49425 ± 13677 (47948)	49505 ± 14656 (47394)	101.2	96.8 – 105.8

Lamivudine

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90%CI (ANOVAlog)
t_{max} (h)	1.98 ± 0.82	1.73 ± 1.01	-	-
C_{max} (ng/mL)	2270 ± 656 (2182)	2566 ± 734 (2446)	89.2	84.8 – 93.8
$AUC_{0\text{-}t}$ (ng.h/mL)	12183 ± 3361 (11766)	13097 ± 3135 (12696)	92.7	89.1 – 96.4
$AUC_{0\text{-}inf}$ (ng.h/mL)	12461 ± 3370 (12049)	13376 ± 3132 (12988)	92.8	89.3 – 96.4

Tenofovir

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	0.86 ± 0.29	0.88 ± 0.44	-	-
C_{max} (ng/mL)	468 ± 113 (454)	465 ± 122 (449)	101.2	95.7 – 107.0
$AUC_{0\text{-}t}$ (ng.h/mL)	3064 ± 801 (2954)	3153 ± 769 (3059)	96.6	93.3 – 100.0
$AUC_{0\text{-}inf}$ (ng.h/mL)	3317 ± 838 (3213)	3402 ± 781 (3289)	97.7	94.5 – 101.0

The results of the study show that the preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding dolutegravir, lamivudine and tenofovir. Accordingly, the test [HA699 trade name] 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® (GlaxoSmithKline), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.).

4. Summary of Product Safety and Efficacy

[HA699 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the WHO recommended comparator products.

According to the submitted data on quality and bioavailability, [HA699 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO-recommended comparator products 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 [HA699 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA699 trade name] has shown to be bioequivalent with Epivir® (ViiV Healthcare Ltd, Canada), Viread® (Gilead Sciences, Germany) and Tivicay® (ViiV Healthcare Ltd, Japan).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA699 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 [HA699 trade name] was acceptable for the following indication: 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 [HA699 trade name] allow inclusion of [HA699 trade name], manufactured at Sun Pharmaceutical Industries Limited, Village Ganguwala, Paonta Sahib, District Sirmour, Himachal Pradesh, 173 025, India, in the list of prequalified medicinal products.