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	[HA752 trade name]*
Manufacturer of Prequalified Product	Celltrion Pharm Inc. 82, 2 Sandan-ro, Ochang-eup Cheongwon-gu, Cheongju-si Chungcheongbuk-do, 28117 Republic of Korea
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium) /lamivudine/ tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations (J05AR27)
Therapeutic indication	[HA752 trade name] is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.

1. Introduction

[HA752 trade name] is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg. Detailed information on the use of this product is described in the summary of product characteristics (SmPC).

[HA752 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 (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 Series No. 953, 2009, Annex 4). This procedure provides an assurance that the APIs, used in the manufacture of [HA752 trade name], are of good quality and manufactured in accordance with WHO Good

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

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 lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, mannitol, sodium starch glycolate, povidone and pigment yellow 42. The commercially sourced proprietary pigment yellow which is included in the tablet formulation is supported by appropriate declarations and controlled by acceptable specifications. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol partially hydrolyzed, titanium dioxide, macrogol/PEG and talc. TSE / BSE free certificates have been provided for the excipients. Lactose and magnesium stearate are of bovine and vegetable origin respectively.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, capsule-shaped, film coated tablet with 'C7' debossed on one side and plain on the other side. The tablets are packaged in a white opaque HDPE bottle, each filled with one or two packets of a 2g silica gel desiccant, and closed with polypropylene child resistant closure.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO recommended comparator products: Tivicay® (dolutegravir) 50mg tablets, Epivir® (lamivudine) 300mg tablets and Viread® (TDF) 300mg tablets. The selection of excipients was based on the qualitative composition of the individual comparator products, suitability to achieve the desired quality target product profile, compatibility with the APIs and literature studies. Pharmaceutical development was planned with a bilayer strategy with TDF and lamivudine in layer-I and dolutegravir sodium in layer-II. For tenofovir disoproxil fumarate wet granulation approach was selected to improve the flowability and lamivudine added extragranularly to the layer-I. To improve solubility wet granulation was also selected for the dolutegravir layer. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for description, identification of the APIs (HPLC and UV with PDA detection) and colorants, average weight, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), water content (KF), residual solvents (GC), elemental impurities and microbial limits. The test methods have been satisfactorily validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The data showed slight degradation for TDF, though all parameters were well within the agreed limits at both storage conditions. 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 2019 according to internationally accepted guidelines:

A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of a fixed dosed combination film-coated test product containing dolutegravir 50 mg, lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg tablets of Celltrion, Inc., Republic of Korea with reference product (R= R1: TIVICAY® (Dolutegravir) 50 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV) + R2: EPIVIR® (Lamivudine) 300 mg tablets manufactured by GlaxoSmithKline for ViiV Healthcare (ViiV) + R3: VIREAD® (Tenofovir disoproxil fumarate) 300 mg tablets manufactured by Gilead Sciences, Inc. (Gilead)) in normal healthy adult human subjects under fasting conditions (study no. CT-G07 1.2).

The objective of the study was to compare the bioavailability of the stated dolutegravir/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg FDC tablet manufactured by/for Celltrion Inc. Republic of Korea (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 50mg/300mg/300mg (dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg) Batch no. DLFTA1802B.
Treatment R:	Reference – 1 tablet Tivicay® (dolutegravir 50 mg) Batch no. 8ZP9194 – 1 tablet Epivir® (lamivudine 300 mg) Batch no. 8ZP8167. – 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg) Batch no. 013187.

An 11-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 24 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 20 ng/mL for dolutegravir, 15 ng/mL for lamivudine and 3 ng/mL for tenofovir.

The study was performed with 62 participants. Data generated from a total of 57 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)	2.48 ± 1.07	2.51 ± 1.15	-	-
C_{max} (ng/mL)	3470 ± 716 (3396)	3080 ± 867 (2967)	114.5	107.6 – 121.8
AUC_{0-t} (ng.h/mL)	63949 ± 17451 (61601)	56202 ± 16057 (53924)	114.3	108.3 – 120.6
AUC_{0-inf} (ng.h/mL)	67373 ± 19240 (64660)	59399 ± 17994 (56714)	114.1	108.3 – 120.3

* 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)	2.25 ± 0.86	1.65 ± 0.87	-	-
C_{max} (ng/mL)	2225 ± 735 (2111)	2292 ± 639 (2211)	95.4	89.7 – 101.5
AUC_{0-t} (ng.h/mL)	12978 ± 3851 (12384)	13031 ± 3559 (12589)	98.4	93.9 – 103.0
AUC_{0-inf} (ng.h/mL)	13257 ± 3866 (12670)	13294 ± 3588 (12856)	98.5	94.2 – 103.1

* 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)	1.13 ± 0.36	0.98 ± 0.44	-	-
C_{max} (ng/mL)	388 ± 101 (374)	389 ± 95 (376)	99.3	93.3 – 105.7
AUC_{0-t} (ng.h/mL)	2921 ± 761 (2821)	2857 ± 673 (2782)	101.3	97.0 – 105.8
AUC_{0-inf} (ng.h/mL)	3124 ± 779 (3027)	3065 ± 706 (2985)	101.3	97.1 – 105.8

* 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 dolutegravir, lamivudine and tenofovir. Accordingly, the test dolutegravir/lamivudine/tenofovir disoproxil fumarate 50 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® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.).

4. Summary of product safety and efficacy

[HA752 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, [HA752 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Tivicay® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA752 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 [HA752 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA752 trade name] has been shown to be bioequivalent with Tivicay® (ViiV Healthcare), Epivir® (ViiV Healthcare) and Viread® (Gilead Sciences, Inc.)

Efficacy and Safety

Regarding clinical efficacy and safety, [HA752 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 [HA752 trade name] was acceptable for the following indication: treatment of human immunodeficiency virus (HIV) infection, and would allow inclusion of [HA752 trade name], manufactured at Celltrion Pharm Inc. 82, 2 Sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea in the list of prequalified medicinal products.