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	[HA702 trade name][*]
Manufacturer of Prequalified Product:	Cipla Limited Unit VII PD II Verna Industrial Estate Verna, Salcette Goa-403 722 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:	[HA702 trade name] is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and adolescents weighing at least 30 kg.

1. Introduction

[HA702 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].

[HA702 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)

Dolutegravir sodium

The API is the sodium salt of dolutegravir. It is very slightly hygroscopic and contains 2 stereogenic carbon centres. The API is manufactured as a pure enantiomer: sodium (4R,12aS)-9-{[(2,4-

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

difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1', 2':4,5]pyrazino[2, 1-b][1,3]oxazin-7 –olate. Extensive spectral studies, including ^{1}H, ^{13}C and ^{19}F with various techniques, have been provided in support of the structure and absolute configuration of the API.

Dolutegravir sodium is critically insoluble (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. The API exhibits (pseudo)polymorphism and it has been demonstrated by X-ray powder diffraction (XRPD) and infrared spectroscopy (IR) that the manufacturing process consistently yields one polymorphic form, called Form I. The acceptance criteria for PSD were set on information of the API lot used in the FPP biobatch.

The API specifications include tests for description, solubility, identification of the API (IR, HPLC) and sodium, water content (KF), heavy metals, isomeric purity (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic identity (XRPD), rhodium content (ICP-MS) and particle size distribution.

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 and HPLC), assay (HPLC), limit of lamivudine enantiomer (HPLC), Other related compounds (HPLC), water determination (KF), light absorption, polymorphic identity (XRPD), residue on ignition, melting range, tapped density, residual solvents (GC), toluene sulfonates (LC-MS; each $\leq$ 5 ppm) and methane sulfonates (GC-MS; each $\leq$ 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, (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. TDF is known to exhibit polymorphism and exists in two forms, namely a low melting form (m.p. 112-114^{0}C) and a high melting form (m.p. 114-118^{0}C). The high melting form, controlled by XRPD and melting point (DSC), is consistently produced.

The specifications for TDF include tests for description, solubility, identification (IR, HPLC), water content (KF), clarity and colour of solution, fumaric acid content (HPLC), heavy metals, assay (HPLC), 9-propenyladenine (HPLC; $\leq$ 5 ppm), polymorphic identity (DSC, XRPD), residual solvents (GC), particle size, enantiomeric purity (chiral HPLC; S-isomer $\leq$ 1.0%) and related substances (HPLC, GC).

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 mannitol, microcrystalline cellulose, sodium starch glycolate, povidone, croscarmellose sodium, magnesium stearate and hydroxypropyl methylcellulose, all being conventional pharmaceutical ingredients complying with the requirements of the pharmacopoeia. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, talc, titanium dioxide, sodium lauryl sulfate, FD& C Blue #2/Indigo carmine and FD& C Blue #1/Brilliant Blue FCF Aluminium lake. 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 blue-coloured, capsule-shaped, biconvex, film-coated tablet, debossed with 'C' on one side and plain on the other side. The tablets are presented in white HDPE bottles with silica gel bags and closed with white non-child resistant caps.

The aim of the development was to formulate an immediate release FDC dosage form, which is stable, pharmaceutically equivalent and bioequivalent to the individual WHO comparator products Tivicay® (Dolutegravir) 50mg Tablets, Epivir® (Lamivudine) 300mg Tablets and Viread® (Tenofovir disoproxil fumarate) 300mg Tablets. The quality target product profile was defined based on the properties of the APIs, consideration of the individual product labels of the comparators and the intended patient population. Wet granulation was selected for the dolutegravir part to improve wettability and flow properties, whilst dry granulation was chosen for the tenofovir part due to its heat and moisture sensitivity. Lamivudine, however, was included extra-granularly in view of its high concentration in the formulation. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics. Based on the satisfactory data of optimization trials, the formula was finalized. 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 colorants, average weight, 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.

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, though the results for all parameters at these storage conditions 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.

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, randomized, open-label, two-way crossover bioequivalence study of [HA702 trade name] (Cipla Ltd., India) and Tivicay® (dolutegravir) 50 mg tablets (ViiV Healthcare), Epivir® (lamivudine) 300 mg tablets (ViiV Healthcare) and Viread® (tenofovir disoproxil fumarate) 300 mg tablets (Gilead Sciences, Inc. USA) in healthy male and female volunteers under fasting conditions (study no. 2118).

The objective of the study was to compare the bioavailability of the stated [HA702 trade name] manufactured by Cipla Ltd., 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 [HA702 trade name]
(dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. GG70245

Treatment R: Reference
– 1 tablet Tivicay® (dolutegravir 50 mg)
Batch no. 5ZP3006.
– 1 tablet Epivir® (lamivudine 300 mg)
Batch no. 5ZP1465
– 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg)
Batch no. 005384

A 14 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 23 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, 50 ng/mL for lamivudine and 5 ng/mL for tenofovir.

The study was performed with 60 participants; data generated from a total of 55 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)	2.62 ± 1.39	2.85 ± 1.48	-	-
C_{max} (ng/mL)	2578 ± 817 (2442)	2734 ± 1133 (2520)	96.9	90.7 – 103.5
AUC_{0-t} (ng·h/mL)	50078 ± 16318 (47261)	54652 ± 20445 (50978)	92.7	87.3 – 98.5
AUC_{0-inf} (ng·h/mL)	53066 ± 17996 (49944)	57456 ± 21740 (53503)	93.4	88.0 – 99.1

Lamivudine

	Test formulation (T)	**Reference (R)**	**log-transformed parameters**

Pharmacokinetic Parameter	arithmetic mean ± SD (geometric mean)	arithmetic mean ± SD (geometric mean)	**Ratio** T/R (%)	**Conventional** 90%CI (ANOVAlog)
t_{max} (h)	1.75 ± 0.86	1.80 ± 0.96	-	-
C_{max} (ng/mL)	2586 ± 842 (2448)	2566 ± 771 (2447)	100.0	94.7 – 105.6
AUC_{0-t} (ng·h/mL)	12112 ± 3767 (11527)	11954 ± 3619 (11437)	100.8	97.3 – 104.4
AUC_{0-inf} (ng·h/mL)	12562 ± 3827 (11981)	12291 ± 3611 (11878)	100.9	97.5 – 104.4

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)	0.96 ± 0.41	0.89 ± 0.43	-	-
C_{max} (ng/mL)	316 ± 128 (294)	322 ± 127 (301)	97.6	91.6 – 104.0
AUC_{0-t} (ng·h/mL)	2531 ± 959 (2377)	2568 ± 962 (2419)	98.2	94.5 – 102.2
AUC_{0-inf} (ng·h/mL)	2757 ± 1039 (2621)	2823 ± 1033 (2669)	98.2	94.9 – 101.6

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 [HA702 trade name] 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

[HA702 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, [HA702 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 [HA702 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA702 trade name] has shown to be bioequivalent with Epivir® (ViiV Healthcare Ltd), Viread® (Gilead Sciences) and Tivicay® (ViiV Healthcare Ltd).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA702 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 [HA702 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 [HA702 trade name] allow inclusion of [HA702 trade name], manufactured at Cipla Limited, Unit VII PD II, Verna Industrial Estate, Verna, Salcette, Goa-403 722, India, in the list of prequalified medicinal products.