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	[HA696 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited, Unit-III (Formulations) Plot #22-110, IDA Jeedimetla, Hyderabad Telangana – 500 055 India
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium)/lamivudine/tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HIV infections, combinations, (J05AR)
Therapeutic indication	[HA696 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

[HA696 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].

[HA696 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-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. Appropriate spectral studies 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

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

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, polymorphic identity (XRPD), water content (KF), related substances (HPLC), assay (HPLC), residual solvents (GC), palladium 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), light absorption, water content (KF), residue on ignition, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.30 %), residual solvents (GC), other related compounds (HPLC), assay (HPLC), polymorphic identity (XRPD), residual solvents (GC), particle size, toluene sulfonates (LC-MS; each ≤ 5 ppm) and methane sulfonates (GC-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. 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), polymorphic identity (XRPD), clarity of solution, water content (KF), heavy metals, melting point, related substances (HPLC),9-propenyladenine (HPLC; ≤ 5 ppm), enantiomeric purity (chiral HPLC; S-isomer ≤ 0.40 %), assay (HPLC), fumaric acid content (HPLC), , residual solvents (GC), particle size and microbial limits.
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, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, sodium starch glycolate, mannitol, povidone 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, talc, iron oxide yellow and iron oxide red. 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 an orange coloured, modified capsule shaped, biconvex film coated tablet debossed with 'H' on one side and 'D' and '17' separated by a score line on other side. The score line is not intended for breaking the tablet. The tablets are presented in white opaque HDPE bottles with silica gel desiccant canisters and cotton space filler and closed with white opaque child resistant polypropylene caps with pulp liners.
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® 50 mg tablets (dolutegravir), Epivir® 300 mg tablets (lamivudine) and Viread® 300 mg tablets (tenofovir disoproxil fumarate). Compatibility studies were conducted between the individual APIs and commonly employed excipients, and on API-API and API-excipient mixtures. Based on these studies it was decided to avoid contact of dolutegravir sodium with lamivudine and tenofovir disoproxil fumarate by developing a bi-layered tablet with dolutegravir sodium in one layer and lamivudine and tenofovir disoproxil fumarate in the other layer.
Direct compression was ruled out because of the poor flow properties of all the three APIs. dolutegravir sodium and lamivudine are introduced through aqueous granulation and tenofovir disoproxil fumarate is 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, HPLC-PDA), 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 at the long-term storage condition though within agreed limits. 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 bioequivalence

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

An open label, balanced, randomized, two-treatment, two- sequence, two-period, single oral dose crossover bioequivalence study of [HA696 trade name] of Hetero Labs Limited, India with the same dose of the individual reference formulations Tivicay® (dolutegravir) 50 mg tablets of GlaxoSmithKline Research Triangle Park, NC 27709; Epivir® (lamivudine) 300 mg tablets of GlaxoSmithKline Research Triangle Park, NC 27709 and Viread® (tenofovir disoproxil fumarate) 300 mg tablets of Gilead Sciences, Inc. Foster City, CA 94404 in healthy, adult, human subjects under fasting conditions. (study no. BE/17/360).

The objective of the study was to compare the bioavailability of the stated [HA696 trade name] manufactured by/for Hetero Labs 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 [HA696 trade name]
(dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. E170754A.

Treatment R: Reference – 1 tablet Tivicay® (dolutegravir 50 mg)
Batch no. 5ZP1936.
– 1 tablet Epivir® (lamivudine 300 mg)
Batch no. 5ZP1465.
– 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg)
Batch no. 004201

A 8 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 29 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 dolutegravir, lamivudine and tenofovir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 28 ng/mL for dolutegravir, 20 ng/mL for lamivudine and 4 ng/mL for tenofovir.

The study was performed with 56 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	3.01 ± 1.60	2.88 ± 1.82	-	-
C_{max} (ng/mL)	2122 ± 780 (2001)	2219 ± 676 (2109)	94.9	85.3 – 105.6
AUC_{0-t} (ng·h/mL)	49314 ± 20732 (45359)	51160 ± 16695 (48165)	94.2	84.9 – 104.5
AUC_{0-inf} (ng·h/mL)	52860 ± 22886 (48434)	54590 ± 18300 (51299)	94.4	85.3 – 104.5

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)	2.11 ± 0.86	1.94 ± 0.85	-	-
C_{max} (ng/mL)	2055 ± 559 (1984)	2052 ± 662 (1946)	101.9	95.5 – 108.9
AUC_{0-t} (ng·h/mL)	11840 ± 2764 (11514)	11717 ± 3327 (11188)	102.9	97.5 – 108.6
AUC_{0-inf} (ng·h/mL)	12124 ± 2722 (11817)	12020 ± 3278 (11533)	102.5	97.5 – 107.7

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)	1.03 ± 0.60	0.93 ± 0.44	-	-
C_{max} (ng/mL)	470 ± 169 (444)	438 ± 145 (415)	106.9	100.2 – 114.0
AUC_{0-t} (ng·h/mL)	3203 ± 779 (3113)	3082 ± 827 (2968)	104.9	99.8 – 110.2
AUC_{0-inf} (ng·h/mL)	3443 ± 827 (3348)	3280 ± 868 (3163)	105.9	101.0 – 111.0

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 [HA696 trade name] 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

[HA696 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, [HA696 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Tivicay® (GlaxoSmithKline), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA696 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 [HA696 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA696 trade name] has been shown to be bioequivalent with Tivicay® (GlaxoSmithKline), Epivir® (GlaxoSmithKline) and Viread® (Gilead Sciences, Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA696 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 [HA696 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 would allow inclusion of [HA696 trade name], manufactured at Hetero Labs Limited, Unit-III (Formulations), Plot #22-110, IDA, Jeedimetla, Hyderabad, Telangana, 500 055, India in the list of prequalified medicinal products.