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	[HA755 trade name][*]
Manufacturer of Prequalified Product	Micro Labs Limited (ML06) Plot No S-155 to S-159 & N1, Phase III & Phase IV Verna Industrial Estate Verna, Goa, 403 722, 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 (J05AR27)
Therapeutic indication	[HA755 trade name] is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.

1. Introduction

[HA755 trade name] is indicated in the treatment of HIV, as detailed in the summary of product characteristics.

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

Dolutegravir sodium, sodium (4R,12aS)-N-(2,4-dif1uorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a hexahydro-2H-pyrido [1',2':4,5] pyrazino[2,1-b] [1,3] oxazine-9-carboxamide) is an off-white to yellow coloured powder. The structure is characterized by FT-IR, UV, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and elemental analysis. The API is BCS critically insoluble. The API possesses two chiral centers and exhibits isomerism. The manufacturer consistently produces the crystalline anhydrous form and in the micronized grade. The polymorphic form-I which is obtained by the FPP manufacturer is confirmed by p-XRD.

The specifications for dolutegravir sodium include tests for description, solubility, identification (IR and HPLC), water content (KF), sodium content, related substances (HPLC), assay (HPLC), residual solvents (GC), polymorphic identity (p-XRD) and particle size distribution.

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

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.

Lamivudine

Based on scientific principles WHO PQTm has identified lamivudine (up to 300 mg oral dose) as a BCS class 3 API. The API is thus BCS highly soluble. 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), limit of lamivudine enantiomer (HPLC; ≤ 0.30%), residual solvents (GC), related substances (HPLC), assay (HPLC), residue on ignition, particle size distribution, mesylates content (GC-MS; each ≤ 5 ppm) and tosilates content (LC-MS/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 of BCS high solubility.

TDF 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 TDF specifications include tests for description, solubility, identification of the API (IR, HPLC), polymorphic form (XRD), clarity of solution, water content (KF), melting point, residue on ignition, related substances (HPLC), enantiomeric purity (S-isomer ≤ 0.4%), assay (HPLC), fumaric acid content, residual solvents (GC) and particle size. The specifications also control the mutagenic 9-propenyladenine, which is a synthesis related substance, at ≤ 5 ppm. This is in accordance with the requirement of tenofovir disoproxil fumarate Ph.Int.

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, sodium starch glycolate, lactose monohydrate, croscarmellose sodium, pregelatinized starch, magnesium stearate, mannitol, FD&C Blue #2/ Indigo carmine aluminium lake, povidone and sodium stearyl fumarate. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, FD&C Blue #2/ Indigo carmine aluminium lake and D&C Yellow #10 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 green-coloured, oblong-shaped, film-coated tablet, debossed with ‘E22’ on one side and plain on the other side. The tablets are packaged in a white, round HDPE bottle with PP child-resistant cap or screw cap and a head induction foil inner seal. The bottle also contains a 1g activated silica gel canister and a white, soft, polyester fibre coil roll.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO comparator products: Tivicay® (dolutegravir) 50mg tablets, Epivir® (lamivudine) 300mg tablets and Viread® (TDF) 300mg tablets. Wet granulation was selected to overcome the poor flow properties of the APIs. A bilayer-tablet approach with separate

granulations of the dolutegravir sodium part forming one layer and the lamivudine part and tenofovir disoproxil fumarate part together, forming the other layer, was adopted. FD&C Blue #2/ Indigo carmine aluminium lake was used as colorant in the dolutegravir sodium part to aid in the identification of the separate tablet layers. The selection of excipients was based on their suitability to achieve the desired tablet characteristics, information of the qualitative composition of the comparator products and compatibility with the APIs. 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.

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 PDA detector) and colorants, water content (KF), average weight, dimensions (thickness, length and width), disintegration time, uniformity of dosage units (by content uniformity), dissolution (HPLC detection), assay (HPLC), related substances (HPLC), 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 indicated some degradation at accelerated conditions, 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 regarded 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, two way crossover, oral bioequivalence study of Dolutegravir, Lamivudine & Tenofovir Disoproxil Fumarate tablets 50/300/300 mg manufactured by Micro Labs Limited, India with Tivicay® (dolutegravir) tablets 50 mg of ViiV Healthcare, Research Triangle Park, NC 27709, EPIVIR® (lamivudine) tablets 300 mg of ViiV Healthcare Research Triangle Park, NC 27709 and VIREAD® (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc. Foster City, CA 94404 in healthy, adult, human subjects under fasting conditions (study no. 016-19).

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 Micro Labs Limited, 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 dolutegravir/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg

(dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. VDAG003.

Treatment R: Reference
– 1 tablet Tivicay®
(dolutegravir 50 mg)
Batch no. 8ZP7933
– 1 tablet Epivir®
(lamivudine 300 mg)
Batch no. 8ZP8167.
– 1 tablet Viread®
(tenofovir disoproxil fumarate 300 mg)
Batch no. 010992.

A 13-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 27 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 tenofovir, lamivudine and dolutegravir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 40 ng/mL for dolutegravir, 25 ng/mL for lamivudine and 4 ng/mL for tenofovir.

The study was performed with 62 participants. Data generated from a total of 60 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)	2.73 ± 1.59	2.28 ± 1.45	-	-
C_{max} (ng/ml)	3357 ± 758 (3273)	3007 ± 870 (2881)	113.6	107.4 – 120.1
AUC_{0-t} (ng.h/ml)	64569 ± 19281 (61843)	56477 ± 16654 (54201)	114.1	108.8 – 119.7
AUC_{0-inf} (ng.h/ml)	68343 ± 21585 (65186)	59651 ± 18550 (57098)	114.2	108.8 – 119.8

* 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)	2.28 ± 0.94	1.69 ± 0.78	-	-
C_{max} (ng/ml)	2113 ± 619 (2025)	2259 ± 652 (2164)	93.6	88.6 – 98.8
AUC_{0-t} (ng.h/ml)	12223 ± 3537 (11732)	12140 ± 3353 (11681)	100.4	95.8 – 105.3
AUC_{0-inf} (ng.h/ml)	12578 ± 3535 (12104)	12468 ± 3375 (12017)	100.7	96.4 – 105.2

* 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)	1.08 ± 0.49	0.84 ± 0.25	-	-
C_{max} (ng/ml)	318 ± 91 (304)	343 ± 82 (333)	91.3	86.5 – 96.5
AUC_{0-t} (ng.h/ml)	2451 ± 696 (2356)	2477 ± 680 (2386)	98.8	94.9 – 102.8
AUC_{0-inf} (ng.h/ml)	2642 ± 726 (2548)	2657 ± 711 (2564)	99.4	95.7 – 103.2

* geometric mean

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 dolutegravir/lamivudine/tenofovir disoproxil fumarate 50mg/300mg/300mg 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

[HA755 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, [HA755 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 [HA755 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 [HA755 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA755 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, [HA755 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 [HA755 trade name] was acceptable for the following indication: **the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.**, and would allow inclusion of [HA755 trade name], manufactured at Micro Labs Limited (ML06), Plot No S-155 to S-159 & N1, Phase III & Phase IV Verna Industrial Estate, Verna, Goa, 403 722, India, in the list of prequalified medicinal products.