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	[HA722 trade name][*]
Manufacturer of Prequalified Product	Emcure Pharmaceuticals Limited Plot No. P1 & P2, I.T.B.T. Park Phase II, MIDC, Hinjawadi, Pune, Maharashtra – 411057 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	[HA722 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

[HA722 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].

[HA722 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

Dolutegravir sodium has 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 API, used in the manufacture of [HA722 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.

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

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, identification (IR and HPLC), melting point (DSC), light absorption, water determination, loss on drying, sulphated ash, residue on ignition, limit of lamivudine enantiomer (chiral HPLC; ≤ 0.30%), other related compounds (HPLC), assay (HPLC), residual solvents (GC), polymorphic identity (PXRD) 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.

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 (PXRD), clarity of solution, water content (KF), heavy metals, melting point (DSC), 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 distribution 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, croscarmellose sodium, povidone, lactose monohydrate, pregelatinized starch, magnesium stearate, mannitol, sodium starch glycolate 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 partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol and talc. 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, capsule shaped, film coated tablet debossed with ‘HP553’ on one side and plain on the other side. The tablets are presented in a white opaque HDPE bottle and closed with white opaque polypropylene child resistant closure with heat seal liner. Each container also contains either a 2 g or 3 g silica gel canister as desiccant.

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® (Dolutegravir 50 mg) tablets, Epivir® (Lamivudine 300 mg) tablets and Viread® (Tenofovir disoproxil fumarate 300 mg)

tablets. The excipients were selected based on the excipients used in the comparator products, and API-excipient compatibility studies. From API-API compatibility studies, significant level of impurity had been observed between tenofovir disoproxil fumarate and dolutegravir API. Hence, the development strategy has been designed as bilayer formulation having tenofovir disoproxil fumarate – lamivudine in the first layer and dolutegravir in the second layer. Based on the comparator product evaluation, API characterization and API- excipient compatibility study, wet granulation was selected for product development. The rationale for selection of granulation by wet granulation is based on the fact that the process gives granules with uniform distribution of APIs, having better flow properties and tablet compression. 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 HPLC- diode array detection), assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), water content (KF), related substances (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 no significant change was observed and the results for all parameters at the 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. The in-use storage period after first opening of the bottle of pack size of 90 tablets 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, single-dose, two-treatment, two- sequence, two period, crossover, bioequivalence study of comparing fixed dose combination of [HA722 trade name] of Emcure Pharmaceuticals Limited, India with Tivicay (dolutegravir) tablets 50 mg and Epivir (lamivudine) tablets 300 mg of ViiV Healthcare Research Triangle Park, NC, 27709 USA and Viread (tenofovir disoproxil fumarate) tablets 300 mg of Gilead Sciences, Inc. Foster City, CA, 94404 USA in normal, healthy, adult human subjects under fasting condition (study no. PCLPL-110-17).

The objective of the study was to compare the bioavailability of the stated [HA722 trade name] manufactured by/for Emcure Pharmaceuticals Ltd., India (test drug) with the reference formulations Tivicay® (ViiV Healthcare Research Triangle Park), Epivir® (ViiV Healthcare Research Triangle Park) 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 [HA722 trade name]
(dolutegravir 50 mg + lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg)
Batch no. EM79015A.

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. 005874.

A 16-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 31 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 20 ng/mL for dolutegravir, 50 ng/mL for lamivudine and 5 ng/mL for tenofovir.

The study was performed with 36 participants; data generated from a total of 34 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)	3.04 ± 1.46	2.83 ± 1.66	-	-
C_{max} (ng/mL)	3057 ± 847 (2952)	2878 ± 814 (2772)	106.5	97.5 – 116.3
AUC_{0-t} (ng·h/mL)	67680 ± 23080 (64408)	62198 ± 17095 (59910)	107.5	100.0 – 115.6
AUC_{0-inf} (ng·h/mL)	72019 ± 26529 (68044)	66373 ± 19813 (63566)	107.0	99.2 – 115.5

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)	2.24 ± 0.98	1.54 ± 0.61	-	-
C_{max} (ng/mL)	2284 ± 647 (2193)	2388 ± 573 (2326)	94.3	87.5 – 101.6
AUC_{0-t} (ng·h/mL)	12916 ± 3691 (12401)	13007 ± 3637 (12505)	99.2	92.2 – 106.7
AUC_{0-inf} (ng·h/mL)	13303 ± 3704 (12815)	13392 ± 3642 (12908)	99.3	93.1 – 105.9

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)	1.32 ± 0.59	1.08 ± 0.50	-	-
C_{max} (ng/mL)	355 ± 107 (339)	372 ± 124 (351)	96.7	90.1 – 103.8
AUC_{0-t} (ng·h/mL)	2904 ± 871 (2769)	2816 ± 767 (2713)	102.1	96.1 – 108.4
AUC_{0-inf} (ng·h/mL)	3133 ± 915 (2997)	3037 ± 792 (2936)	102.1	96.8 – 107.6

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax values regarding dolutegravir, lamivudine and tenofovir. Accordingly, the test [HA722 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 Research Triangle Park), Epivir® (ViiV Healthcare Research Triangle Park) and Viread® (Gilead Sciences, Inc.).

4. Summary of product safety and efficacy

[HA722 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, [HA722 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator products Tivicay® (ViiV Healthcare Research Triangle Park), Epivir® (ViiV Healthcare Research Triangle Park) and Viread® (Gilead Sciences, Inc.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA722 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 [HA722 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA722 trade name] has been shown to be bioequivalent with Tivicay® (ViiV Healthcare Research Triangle Park), Epivir® (ViiV Healthcare Research Triangle Park) and Viread® (Gilead Sciences, Inc.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA722 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 [HA722 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 [HA722 trade name], manufactured at Emcure Pharmaceuticals Limited, Pune, Maharashtra-411057, India in the list of prequalified medicinal products.