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	[HA688 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited, Plot no: 11-12 & 13, Indore SEZ Pharma Zone, Phase-II, Sector-III Pithampur –454775 Dist. Dhar Madhya Pradesh 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	[HA688 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

[HA688 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].

[HA688 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 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 these APIs, used in the manufacture of [HA688 trade name], are of good quality and manufactured in accordance with WHO good manufacturing practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance

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

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 mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, lactose monohydrate, croscarmellose sodium and magnesium stearate, 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 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, film coated, capsule shaped, biconvex bevelled edge tablet debossed with M on one side and LTD on the other side of the tablet. The tablets are presented in round blue opaque HDPE bottles closed with blue opaque polypropylene caps along with a desiccant.

The tablets have been developed as immediate release tablets based on previous experience. Dolutegravir sodium and tenofovir disoproxil fumarate have been introduced in separate granulates. Dolutegravir sodium has very poor flow properties, hence a wet granulation process was selected to improve blend flow, API distribution and dissolution. As Tenofovir disoproxil fumarate has very poor flow properties, dry granulation by roll compaction process was selected to improve the flow. Lamivudine, however, has acceptable flow properties, and was therefore incorporated in the extra granular portion along with flowable excipients thus ensuring the flow and API distribution of the components throughout the blend. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include tests for description, identification (HPLC), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), water content (KF) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions 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. The in-use storage period 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 2016 according to internationally accepted guidelines.

Single-dose fasting bioequivalence study of [HA688 trade name] (Mylan) versus Epivir® tablets (300 mg; ViiV), Viread® tablets (300 mg; Gilead) and Tivicay® tablets (50 mg; ViiV) in healthy adult volunteers (study no. LTDD-16030).

The objective of the study was to compare the bioavailability of the stated [HA688 trade name] manufactured by Mylan Laboratories, Ltd, India (test drug) with the reference formulations Epivir® (ViiV), Viread® (Gilead) and Tivicay® (ViiV) 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 [HA688 trade name]
(lamivudine 300 mg + tenofovir disoproxil fumarate 300 mg + dolutegravir 50 mg)
Batch no. 2011640

Treatment R: References – 1 tablet Epivir®
(lamivudine 300 mg)
Batch no. 4ZP5151
– 1 tablet Viread®
(tenofovir disoproxil fumarate 300 mg)
Batch no. 003015
– 1 tablet Tivicay® (dolutegravir 50 mg)
Batch no. 5ZP3006

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 21 samples within 72 hours post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax for bioequivalence evaluation. Drug concentrations for lamivudine, tenofovir and dolutegravir were analyzed using validated LC-MS/MS methods. The limit of quantification was stated to be about 25 ng/mL for lamivudine, 3 ng/mL for tenofovir and 40 ng/mL for dolutegravir.

The study was performed with 36 participants; data generated from a total of 31 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for lamivudine, tenofovir and dolutegravir as well as statistical results are summarised in the following tables:

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)	1.97 ± 0.93	1.79 ± 0.80	–	–
C_{max} (ng/mL)	2292 ± 787 (2178)	2421 ± 746 (2332)	93.4	87.0 – 100.2
AUC_{0-t} (ng·h/mL)	11106 ± 2501 (10851)	11772 ± 2683 (11524)	94.2	89.3 – 99.3
AUC_{0-inf} (ng·h/mL)	11501 ± 2501 (11249)	12236 ± 2995 (11936)	94.2	89.0 – 99.8

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)	0.95 ± 0.32	0.86 ± 0.33	-	-
C_{max} (ng/mL)	314 ± 80 (305)	318 ± 83 (308)	98.9	91.9 – 106.4
AUC_{0-t} (ng·h/mL)	2302 ± 528 (2255)	2314 ± 586 (2252)	100.1	96.5 – 103.8
AUC_{0-inf} (ng·h/mL)	2462 ± 537 (2415)	2466 ± 626 (2404)	100.5	97.4 – 103.7

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)	2.77 ± 0.94	2.90 ± 2.06	-	-
C_{max} (ng/mL)	2531 ± 532 (2481)	2606 ± 753 (2485)	99.8	93.8 – 106.3
AUC_{0-t} (ng·h/mL)	51619 ± 12965 (50281)	52871 ± 20604 (49625)	101.3	95.4 – 107.6
AUC_{0-inf} (ng·h/mL)	54883 ± 15004 (53246)	55492 ± 22113 (51999)	102.4	96.6 – 108.6

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding lamivudine, tenofovire and dolutegravir. Accordingly, the test [HA688 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Epivir® (ViiV), Viread® (Gilead) and Tivicay® (ViiV).

4. Summary of product safety and efficacy

[HA688 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, [HA688 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Epivir® (ViiV), Viread® (Gilead) and Tivicay® (ViiV) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HA688 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 [HA688 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA688 trade name] has been shown to be bioequivalent with Epivir® (ViiV), Viread® (Gilead) and Tivicay® (ViiV).

Efficacy and Safety

Regarding clinical efficacy and safety, [HA688 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 [HA688 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 [HA688 trade name], manufactured at Mylan Laboratories Limited, Plot No: 11-12 & 13, Indore SEZ, Pharma Zone, Phase-II, Sector-III, Pithampur 454775, Dist. Dhar, Madhya Pradesh, India in the list of prequalified medicinal products.