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	[HA737 trade name][*]
Manufacturer of Prequalified Product	Lupin Limited Plot No. 6A1, 6A2, Sector-17 Special Economic Zone MIHAN Notified Area Nagpur Maharashtra-441108 India
Active Pharmaceutical Ingredient(s) (API)	Dolutegravir (as sodium) / Lamivudine / Tenofovir disoproxil fumarate
Pharmaco-therapeutic group (ATC Code)	Direct acting antivirals, Antivirals for treatment of HIV infections, combinations (J05AR27)
Therapeutic indication	[HA737 trade name] is indicated for the treatment of human immunodeficiency virus (HIV) infection in adults and adolescents weighing at least 30 kg.

1. Introduction

[HA737 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 Ingredient (API)

Dolutegravir sodium

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 a white to light yellow 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 centres 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, enantiomer content (HPLC), assay (HPLC), related

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

substances (HPLC), residual solvents (GC and GC-MS), polymorphic identity (p-XRD), particle size distribution, methanesulfonates (methyl, ethyl and propyl; by GC-MS ≤ 14.2ppm) 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.

Lamivudine and tenofovir disoproxil fumarate

Lamivudine and tenofovir disoproxil fumarate (TDF) 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 the APIs, used in the manufacture of [HA737 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.

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, microcrystalline cellulose, povidone, lactose monohydrate, croscarmellose sodium, hypromellose, colloidal silicon dioxide, talc, magnesium stearate and sodium starch glycolate, all being pharmacopoeia controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol-partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol and talc. TSE / BSE free certificates have been provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white, biconvex modified capsule-shaped, bevelled edge, film coated tablet debossed with 'L160' on one side and plain on the other side.

The tablets are packaged in a white, opaque, round, HDPE bottle with a berry or triveni VBC child resistant closure (white, round polypropylene) with heat seal printed liner. The bottle also contains two or three 5g molecular sieve sachets.

The objective of the development programme was to obtain a stable, robust, immediate-release FDC tablet that is bioequivalent to the WHO recommended comparator products: Tivicay® (dolutegravir) 50mg tablets, Epivir® (lamivudine) 300mg tablets and Viread® (TDF) 300mg tablets. The selection of excipients was based on their similarity to those of the comparator products, suitability to achieve the desired quality target product profile, compatibility with the APIs and literature studies. Wet granulation was selected for dolutegravir and lamivudine parts and dry granulation by roller compaction was selected for tenofovir disoproxil fumarate to ensure good flow of the blend and better uniformity of the non-bilayer tablets. Formulation trials were performed to optimise the concentration of excipients and process parameters. Satisfactory in-process controls have been established.

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 TLC), water content (KF), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), assay (HPLC), related substances (HPLC), residual solvent, limit of s-isomer of TDF (HPLC), limit of enantiomers of dolutegravir and lamivudine (HPLC), 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 showed slight degradation for TDF, 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 acceptable. The in-use storage period after first opening of the bottles 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 2018 according to internationally accepted guidelines:

A randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover bioequivalence study comparing test product; dolutegravir, lamivudine and tenofovir disoproxil fumarate tablets 50 mg/300mg/300mg of Lupin Limited, India, with individual reference products; Tivicay® (dolutegravir sodium) tablets 50mg of ViiV Health Care, Research Triangle Park, NC27709, EPIVIR® (lamivudine) tablets 300mg of ViiV Health Care, Research Triangle Park, NC27709 and Viread® (tenofovir disoproxil fumarate) tablets 300mg of Gilead Sciences Inc. Foster City. CA 94404 in normal, healthy, adult, male human subjects under fasting conditions (study no. ARL/17/584 (LBC-18-060).

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 Lupin 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. M890080

Treatment R: Reference
– 1 tablet Tivicay® (dolutegravir 50 mg), batch no. 7ZP0505
– 1 tablet Epivir® (lamivudine 300 mg), batch no. 6ZP7456
– 1 tablet Viread® (tenofovir disoproxil fumarate 300 mg), batch no. 005882

A 7-day wash-out period was observed between administration of the 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 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, 20 ng/mL for lamivudine and 4 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)	2.37 ± 1.14	2.39 ± 0.94	-	-
C_{max} (ng/mL)	3114 ± 830 (2988)	2817 ± 754 (2718)	110.0	99.8 – 121.2
AUC_{0-t} (ng.h/mL)	57586 ± 21256 (53248)	53869 ± 19305 (50002)	106.5	96.7 – 117.3
AUC_{0-inf} (ng.h/mL)	59904 ± 23082 (55135)	55870 ± 20145 (51798)	106.4	96.7 – 117.2

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)	2.10 ± 0.79	1.57 ± 0.63	-	-
C_{max} (ng/mL)	2281 ± 605 (2215)	2517 ± 589 (2457)	90.1	84.9 – 95.6
AUC_{0-t} (ng.h/mL)	12650 ± 2829 (12353)	12962 ± 2590 (12716)	97.1	92.1 – 102.4
AUC_{0-inf} (ng.h/mL)	12984 ± 2848 (12690)	13303 ± 2616 (13058)	97.2	92.4 – 102.2

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)	1.11 ± 0.45	0.82 ± 0.29	-	-
C_{max} (ng/mL)	399 ± 95 (388)	421 ± 101 (409)	94.8	88.5 – 101.5
AUC_{0-t} (ng.h/mL)	3090 ± 839 (2958)	3135 ± 849 (3028)	97.7	90.5 – 105.5
AUC_{0-inf} (ng.h/mL)	3309 ± 896 (3175)	3353 ± 924 (3236)	98.1	91.2 – 105.6

The results of the study show that the pre-set 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

[HA737 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, [HA737 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product 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 [HA737 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 [HA737 trade name] is used in accordance with the SmPC.

Bioequivalence

[HA737 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, [HA737 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 [HA737 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 [HA737 trade name], manufactured at Lupin Limited, Plot No. 6A1, 6A2, Sector-17, Special Economic Zone, MIHAN Notified Area, Nagpur, Maharashtra-441108, India in the list of prequalified medicinal products.