CLINICAL PHARMACOLOGY REVIEW

NDA	22141
Submission Type	505(b)(2)
Submission Date	08/31/2017
Generic Name	Lamivudine (3TC)/ Tenofovir Disoproxil Fumarate (TDF)
Brand Name	CIMDUO™
Indication	Treatment of HIV
Dosage Form/ Strength	Fixed Dose Combination Tablet: 3TC (300 mg)/ TDF (300 mg)
Applicant	Mylan
Review Team	Islam R. Younis, Ph.D.

Background

The 3TC/TDF (300 mg/ 300 mg) fixed dose combination (FDC) tablet was tentatively approved on 09/12/2008 under the provisions of the President's Emergency Plan for AIDS Relief (PEPFAR) program. In this submission, the applicant is requesting final approval of the FDC following the expiration of the pediatric exclusivity associated with U.S. Patent Nos. 5,922,695; 5,935,946; 5,977,089; and 6,043,230; following the expiration of the pediatric exclusivity associated with the orphan drug exclusivity that expired in 2017 for Viread®; and prior to the D-147 (Epivir's exclusivity granted for QD dosing in pediatric patients) marketing exclusivity. D-147 marketing exclusivity was set to expire in March 2018, however, the Orange Book staff and OCC recently determined this exclusivity was granted in error and removed it.

Summary of Clinical Pharmacology Findings

The applicant conducted two relative bioavailability studies under fasted (Study 234-17) and fed (Study 235-17) conditions to compare 3TC and TDF exposures following the administration of the 3TC/TDF FDC tablet and the individual TDF (VIREAD®) and 3TC (EPIVIR®) agents administered in combination. These studies were conducted due to the multiple amendment to the chemistry, manufacturing, and controls post receipt of the tentative approval (Please refer to application and CMC review for more information). The exposures of 3TC and TDF were similar following the administration of the FDC relative to the individual agents (Table 1). The Office of Study Integrity and Surveillance (OSIS) declined the request to inspect the clinical and analytical sites of the abovementioned studies because these sites were inspected recently and the inspection outcome was "No Action Needed". OSIS recommended accepting study data (Please see OSIS memorandum dated 11/03/2017).

Drug	PK Parameter	Study 234-14 (Fasted, n=44) GMR (90% CI)	Study 235-14(Fed, n=35) GMR (90% CI)
3TC	$AUC_{0-\infty}$ (ng h/mL)	0.97 (0.92, 1.00)	1.0 (0.94, 1.06)
	Cmax (ng/mL)	0.88 (0.83, 0.94)	0.95 (0.88, 1.03)
Tenofovir	$AUC_{0-\infty}$ (ng h/mL)	1.0 (0.98, 1.03)	0.96 (0.92, 0.99)
	Cmax (ng/mL)	1.0 (0.93, 1.09)	0.86 (0.82, 0.91)

Recommendations

The application is recommended for approval from clinical pharmacology perspective.

Labeling Recommendations

The (b) (4) information regarding (b) (4) were removed because (b) (4).

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INDIVIDUAL STUDIES REVIEW

Study #	234-17	Study Period	04/18/2015-05/01/2015	EDR Link
Title	A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, bioequivalence study of Fixed dose combination tablets of Tenofovir Disoproxil Fumarate / Lamivudine 300 mg/300 mg manufactured by Mylan Laboratories limited, India with VIREAD® (Tenofovir Disoproxil Fumarate) 300 mg Tablets manufactured by Gilead Sciences, Inc. Foster City, CA 94404 and EPIVIR® (Lamivudine) 300 mg tablets of Glaxosmithkline Research Triangle Park, NC 27709, manufactured for Viiv Healthcare, Research Triangle Park, NC 27709 in healthy human adult male and/or female subjects, under fasting conditions.			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To compare 3TC and TFV exposures following the administration of 3TC/TDF FDC vs. the simultaneous administration of Viread® and Epivir®

Rationale: The study was conducted due to multiple amendment to the CMC of the FDC following tentative approval.

Dose Selection: Selected dose are the therapeutic doses of 3TC (300 mg) and TDF (300 mg)

Design and PK Assessments:

- A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two-way crossover study with a 9 days washout period.
- Serial blood samples for determination of plasma concentrations of 3TC and TFV were collected for 72 following administration of test and reference drugs.

Population: ☑ Healthy Subjects ☐ Patients | Administration: ☑ Fasted ☐ Fed

Formulations: Reference products are commercially available RLD for 3TC (Epivir®) and TDF (Viread®). Test product is the 3TC/TDF FDC manufactured by Mylan at the Aurangabad facility. .

RESULTS

Enrolled	44	Completed	44	Discontinued Due to AE	0	PK Population	44	Safety Population	44

Bioanalytical Method: Link to Study Samples Analysis **and** Validation Report

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TFV		3TC
Range (ng/mL)	5.033 – 600.408		24.009 – 4081.59

Protocol Deviations: No major deviations were reported.

- Deviations in PK sampling were reported in 6 incidences across 6 subjects where PK samples were collected within 7 minutes (range +2 to +7 minutes) of the scheduled time.
- The temperature of deep freezer rose up to -48 ˚C for about 7.5 hours during study samples storage.

Pharmacokinetics (data copied from CSR pages 11 and 15)

Summary of Bioequivalence Parameters of Tenofovir for ln-transformed data

Parameter	N	Geometric LSM		(A/B1) Ratio (%)	ISCV%	Power	90% Confidence Intervals
		Test product (A)	Reference product (B1)				
C_{max} (ng/mL)	42	286.870	300.585	95.44	21.828	99.80	(88.16, 103.31)
AUC_{0-t} (ng.h/mL)	42	2162.968	2157.339	100.26	17.798	99.99	(93.96, 106.98)
$AUC_{0-\infty}$ (ng.h/mL)	42	2415.398	2417.854	99.90	16.632	100.0	(94.02, 106.15)

Two subjects (#003 and #022) had 3 missing samples in Period 1 and 2, respectively. These subjects reported a concentration above the LLOQ level for the same time points in the other period. Therefore, these subjects were excluded from statistical analysis of TFV per study protocol.

Summary of Bioequivalence Parameters of Lamivudine for ln-transformed data							
Parameter	N	Geometric LSM		(A/B2) Ratio (%)	ISCV%	Power	90% Confidence Intervals
		Test product (A)	Reference product (B2)				
C_{max} (ng/mL)	44	2291.801	2598.143	88.21	18.449	99.99	(82.61, 94.19)
AUC_{0-t} (ng.h/mL)	44	12706.778	13190.776	96.33	13.295	100.0	(91.87,101.01)
$AUC_{0-\infty}$ (ng.h/mL)	44	13050.492	13524.953	96.49	12.765	100.0	(92.19,100.99)

Two subjects (#003 and #022) had 3 missing samples in Period 1 and 2, respectively. These subjects reported a concentration below the LLOQ level for the same time points in the other period. Therefore, these subjects were included in pharmacokinetic analysis and statistical analysis of 3TC per the study protocol.

Safety: There were no deaths, other serious adverse events or other clinically relevant adverse events reported in the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion: Study results demonstrated that under fasting condition the proposed 3TC/TDF FDC produces exposure of 3TC and TFV similar to those observed following the administration of the individual 3TC and TDF RLD

Study #	235-17	Study Period	04/23/2015-05/04/2015	EDR Link
Title	A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two way crossover, bioequivalence study of Fixed dose combination tablets of Tenofovir Disoproxil Fumarate / Lamivudine 300 mg/300 mg manufactured by Mylan Laboratories limited, India with VIREAD® (Tenofovir Disoproxil Fumarate) 300 mg Tablets manufactured by Gilead Sciences, Inc. Foster City, CA 94404 and EPIVIR® (Lamivudine) 300 mg tablets of Glaxosmithkline Research Triangle Park, NC 27709, manufactured for Viiv Healthcare, Research Triangle Park, NC 27709 in healthy human adult male and/or female subjects, under fed conditions.			

TRIAL SUMMARY (As Reported by the Applicant)

OBJECTIVES, RATIONALE, TRIAL DESIGN AND PK ASSESSMENTS

Objectives: To compare 3TC and TFV exposures following the administration of 3TC/TDF FDC vs. the simultaneous administration of Viread® and Epivir®

Rationale: The study was conducted due to multiple amendment to the CMC of the FDC following tentative approval.

Dose Selection: Selected dose are the therapeutic doses of 3TC (300 mg) and TDF (300 mg)

Design and PK Assessments:

- A randomized, open label, balanced, two treatment, two period, two sequence, single dose, two-way crossover study with a 7 days washout period.
- Serial blood samples for determination of plasma concentrations of 3TC and TFV were collected for 72 following administration of test and reference drugs.

Population: ☑ Healthy Subjects ☐ Patients | Administration: ☐ Fasted ☑ Fed

Formulations: Reference products are commercially available RLD for 3TC (Epivir®) and TDF (Viread®). Test product is the 3TC/TDF FDC manufactured by Mylan at the Aurangabad facility.

RESULTS

Enrolled	44	Completed	35	Discontinued Due to AE	5	PK Population		Safety Population	

Subject # 015, 016, 023, 025 & 027 withdrawn from the study due to AE (Vomiting) in period 1. Subject # 020, 032,039 & 040 dropped out from the study in period 2.

Bioanalytical Method: Link to Study Samples Analysis **and** Validation Report

Method Type	LC-MS/MS	Matrix	Plasma
Analytes	TFV		3TC
Range (ng/mL)	5.033 – 600.408		24.009 – 4081.59

Protocol Deviations: No major deviations were reported.

- Deviations in PK sampling were reported in 4 incidences across 4 subjects where PK samples were collected up to 21 minutes (range +2 to +21 minutes) of the scheduled sampling time.
- The temperature of deep freezer rose up to -48 ˚C for about 7.5 hours during study samples storage.

Pharmacokinetics (data copied from CSR pages 11 and 15)

Summary of Bioequivalence Parameters of Tenofovir for ln-transformed data

Parameter	N	Geometric LSM		(A/B1) Ratio (%)	ISCV%	Power	90% Confidence Intervals
		Test product (A)	Reference product (B1)				
C_{max} (ng/mL)	33	305.927	303.251	100.88	19.349	99.76	(93.12,109.29)
AUC_{0-t} (ng.h/mL)	33	3200.252	3178.706	100.68	7.695	100.0	(97.50,103.96)
$AUC_{0-\infty}$ (ng.h/mL)	33	3439.763	3431.606	100.24	6.580	100.0	(97.52,103.03)

Two subjects (#004 and #008) had 3 missing samples in Period 1. These subjects reported a concentration above the LLOQ level for the same time points in Period 2. Therefore, these subjects were excluded from statistical analysis of TFV per study protocol.

Summary of Bioequivalence Parameters of Lamivudine for ln-transformed data							
Parameter	N	Geometric LSM		(A/B2) Ratio (%)	ISCV%	Power	90% Confidence Intervals
		Test product (A)	Reference product (B2)				
C_{max} (ng/mL)	35	1959.404	2281.011	85.90	14.437	100.0	(81.05, 91.04)
AUC_{0-t} (ng.h/mL)	35	11862.105	12480.571	95.04	9.135	100.0	(91.60, 98.62)
$AUC_{0-\infty}$ (ng.h/mL)	35	12219.384	12784.616	95.58	8.809	100.0	(92.24, 99.04)

Two subjects (#004 and #0008) had 3 missing samples in Period 1. These subjects reported a concentration below the LLOQ level for the same time points in Period 2. Therefore, these subjects were included in pharmacokinetic analysis and statistical analysis of 3TC per the study protocol.

Safety: There were no deaths, other serious adverse events or other clinically relevant adverse events reported in the study.

REVIEWER ASSESSMENT

The study design is acceptable ☑ Yes ☐ No

Study Conduct

- Bioanalytical method performance in acceptable ☑ Yes ☐ No
- Protocol deviations do not affect the integrity of the study ☑ Yes ☐ No

Study Results

The study results are acceptable as reported by the sponsor ☑ Yes ☐ No

Discussion: Study results demonstrated that under fed condition the proposed 3TC/TDF FDC produces exposure of 3TC and TFV similar to those observed following the administration of the individual 3TC and TDF RLD.

Meal composition was not reported in the clinical study report. The report mentions administering the test and reference drugs after consuming high calories, high fat standard breakfast. It is not clear why the applicant conducted the study as both drugs can be taken without regard to food and Study 234-17 would have been sufficient to support approval. It would have been better if the applicant evaluated the effect of food on the FDC.

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/s/

ISLAM R YOUNIS
02/27/2018