CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022344Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-344
Pharma	Lamivudine/Tenofovir Disoproxil Fumarate
Formulation; Strength(s)	300 mg/300 mg tablet
Indication	Treatment of HIV-1 infection
Applicant	Aurobindo Pharma Limited
Reviewer	Assadollah Noory, Ph.D.
Team Leader	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Stamp Date	March 9, 2010

Table of Contents

1. EXECUTIVE SUMMARY

Under the provisions of 505(b)2, Aurobindo Pharma Limited, India is seeking approval for their combination product tenofovir disoproxil fumarate /lamivudine (300 mg / 300 mg) tablet for the treatment of HIV-1 infected patients. This application was submitted under the President's Emergency Plan for AIDS Relief (PEPFAR) initiative. In support of the approval, the applicant submitted two bioequivalence studies assessing the performance of their product versus the US reference listed products, Viread® and Epivir® under fasted and fed conditions.

1.1. Recommendation

The clinical pharmacology information provided in this NDA is acceptable. NDA 22-344 is approvable.

1.2. Phase IV Commitments

There is no phase 4 requirement.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

This application for tenofovir disoproxil fumarate / lamivudine (300 mg /300 mg) combination tablet includes two bioequivalence study reports. Study 199/09 was conducted under fasting conditions and study 200/09 under fed conditions. Both studies were randomized, open-label, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence studies assessing the bioequivalence between the combination product by Aurobindo Pharma Limited (300 mg tenofovir disoproxil fumarate/300 mg lamivudine) to Viread® (tenofovir disoproxil fumarate 300 mg tablets), plus Epivir® (lamivudine 300 mg tablets) in healthy adult subjects.

Single-Dose Fasting Bioequivalence Study (199/09)

Thirty-five subjects completed this two-treatment, two-period, two-sequence, single-dose, crossover, fasting bioequivalence study. The statistical analysis was carried out by this reviewer using SAS 9.2. Plasma PK parameter estimates (arithmetic mean ± SD, geometric mean), point estimates as ratio of test over reference, and the 90% confidence intervals for tenofovir and lamivudine following administration of a single dose under fasting conditions are presented in the following table.

Table 1: Summary Statistics (study 199/09)

(mean +/- SD), Geometric Mean, Point Estimate (T/R), and 90% Confidence Interval						
Parameter	**Test**		**Reference**		**Point Estimate & 90% C. I.**	
Lamivudine						
Cmax (ng/mL)	2133.38 ± 608.53	2046.23	2194.19 ± 518.92	2131.70	95.99	91.32 – 100.97
AUC_{0-t} (ng•h/mL)	12714.70 ± 2964.89	12353.34	12617.46 ± 3050.13	12284.74	100.56	96.01 – 105.34
$AUC_{0-\infty}$ (ng•h/mL)	12944.46 ± 3006.37	12579.92	12853.72 ± 3107.42	12516.83	100.50	95.98 – 105.21
Tenofovir						
Cmax (ng/mL)	370 57 ± 121.04	352 19	389.76 ± 99.09	378.30	93.70	86.03 – 100.92
AUC_{0-t} (ng•h/mL)	2652.34 ± 814.38	2532.19	2682.19 ± 795.33	2570.63	98.50	94.46 – 102.74
$AUC_{0-\infty}$ (ng•h/mL)	2907.02 ± 904.62	2774.23	2933.79 ± 909.30	2806.79	98.84	94.93 – 102.88
Treatments						
Test:	Combination product, Batch number LLTSA09001 by Aurobindo Pharma Limited, India					
Reference:	Epivir®, Batch number 6H001 by GSK , USA					
	Viread®, Batch number A171141D by Gilead Sciences Inc., USA					

The 90% confidence interval for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max}, indicating that the combination tablets are bioequivalent to Viread® plus Epivir®. The results of study 199/09 indicate that the tenofovir disoproxil fumarate / lamivudine 300/300 mg combination tablets provide acceptable exposure compared to Viread® and Epivir® under fasting conditions.

Single-Dose Fed Bioequivalence Study (200/09)

Thirty-four subjects completed this two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study under fed conditions. Plasma PK parameter estimates (arithmetic mean ± SD, geometric mean), point estimates as ratio of test over reference, and the 90% confidence intervals for tenofovir and lamivudine following administration of a single dose under fed conditions are presented in the following table.

Table 2: Summary Statistics (study 200/09)

(mean +/- SD), Geometric Mean, Point Estimate (T/R), and 90% Confidence Interval						
Parameter	**Test**		**Reference**		**Point Estimate & 90% C. I.**	
Lamivudine						
Cmax (ng/mL)	2112.42 ± 561.91	2033.59	2235.48 ± 547.11	2174.17	93.53	86.68 – 100.89
AUC_{0-t} (ng•h/mL)	12264.01 ± 2763.25	11940.67	12313.24 ± 728.83	12020.47	99.34	94.93 – 103.98
$AUC_{0-\infty}$ (ng•h/mL)	12472.34 ± 2777.68	12155.06	12552.78 ± 2732.99	12264.66	99.11	94.93 – 103.46
Tenofovir						
Cmax (ng/mL)	363.10 ± 110.17	346.41	380.67 ± 120.59	356.49	97.17	88.81 – 106.32
AUC_{0-t} (ng•h/mL)	3031.07 ± 688.01	2931.88	2946.62 ± 818.77	2733.13	107.27	98.52 – 116.80
$AUC_{0-\infty}$ (ng•h/mL)	3317.08 ± 752.93	3212.23	3233.20 ± 902.99	3000.63	107.05	98.14 – 116.78
Treatments						
Test:	Combination product, Batch number LLTSA09001 by Aurobindo Pharma Limited, India					
Reference:	Epivir®, Batch number 6H001 by GSK , USA					
	Viread®, Batch number A171141D by Gilead Sciences Inc., USA					

The 90% confidence interval for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max}, indicating that tenofovir and lamivudine combination tablets are bioequivalent to Viread® plus Epivir®. The results of study 200/09 indicate that the tenofovir/ lamivudine 300/300 mg combination tablets provide acceptable exposure compared to Viread® and Epivir® under fed conditions.

The results of study 199/09 and 200/09 indicate that the tenofovir/ lamivudine 300/300 mg combination tablets provide acceptable exposure compared to Viread® and Epivir® under both fasting and fed conditions. The combined results of the fasted and fed bioequivalence studies indicate that the effect of food on the bioavailability of tenofovir and lamivudine from the combination tablet is similar to the effect observed for the marketed Viread® and Epivir® formulations. Thus, the combination tablets may be administered under fed or fasted conditions, like the innovator products.

DSI inspection:

The DSI inspection report of APL Research Center, Bachupally Billage, Quthubullapur Mandal, Hyderabad, India concluded the following:

Study 199/09: Tenofovir, 11 subjects with unreliable data (subjects (b) (6) (b) (6)); additional unreliable data are (listed as subject # and period # (b) (6) (b) (6)).

Unreliable data for lamivudine are ((b) (6) (b) (6)).

Study 200/09: Unreliable data for tenofovir are ([redacted] (b) (6)). Unreliable data for lamivudine are ([redacted] (b) (6)).

The lack of a good quality control program raised the concern about the validity of data results for some subjects in this submission as discussed in the DSI review dated July 9, 2010. Therefore these data could not be used in the statistical analysis of studies 199/09 and 200/09.

A reanalysis of the study was carried out by the reviewer excluding the data from subjects noted above. The results of this reanalysis are shown in the following two tables.

Table 3: Reanalysis, Summary Statistics (study 199/09)

(mean +/- SD), Geometric Mean, Point Estimate (T/R), and 90% Confidence Interval						
Parameter					**Point Estimate & 90% C. I.**	
Lamivudine	**Test (N=30)**		**Reference (N=29)**			
Cmax (ng/mL)	2036.38 ± 575.16	1956.63	2127.36 ± 516.93	2064.33	94.78	89.32 – 101.05
AUC_{0-t} (ng•h/mL)	12403.83 ± 3047.90	12025.57	12601.53 ± 3276.99	12223.00	98.38	92.82 – 103.67
$AUC_{0-\infty}$ (ng•h/mL)	12626.98 ± 3085.43	12246.44	12851 ± 3344.55	12466.24	98.24	92.96 – 103.67
Tenofovir	**Test (N=19)**		**Reference (N=19)**			
Cmax (ng/mL)	376.09 ± 115.14	360 57	367.64 ± 99.87	355.70	101.37	90.94 – 108.98
AUC_{0-t} (ng•h/mL)	2569.70 ± 817.30	2451.56	2315.70 ± 603.01	2239.63	109.46	94.08 – 108.98
$AUC_{0-\infty}$ (ng•h/mL)	2835.26 ± 893.59	2709.78	2524.04 ± 654.18	2444.15	110.87	95.50 – 108.76
Treatments						
Test:	Combination product, Batch number LLTSA09001 by Aurobindo Pharma Limited, India					
Reference:	Epivir®, Batch number 6H001 by GSK , USA					
	Viread®, Batch number A171141D by Gilead Sciences Inc., USA					

Table 4: Reanalysis, Summary Statistics (study 200/09)

(mean +/- SD), Geometric Mean, Point Estimate (T/R), and 90% Confidence Interval						
Parameter					**Point Estimate & 90% C. I.**	
Lamivudine	**Test (N=28)**		**Reference (N=33)**			
Cmax (ng/mL)	2153.13 ± 501.77	2096.96	2222.52 ± 550.26	2160.84	97.04	90.76 – 103.87
AUC_{0-t} (ng•h/mL)	12489.01 ± 2351.09	12280.20	12334.34 ± 2768.32	12032.91	102.06	96.27 – 105.53
$AUC_{0-\infty}$ (ng•h/mL)	12699.77 ± 2380.34	12491.13	12575 ± 2772.23	12278.45	101.73	96.18 – 104.81
Tenofovir	**Test (N=32)**		**Reference (N=24)**			
Cmax (ng/mL)	370.43 ± 108.73	354.36	374.06 ± 117.36	348.04	101.82	89.14 – 113.54
AUC_{0-t} (ng•h/mL)	3049.08 ± 689.65	2948.51	2975.12 ± 850.59	2712.65	108.69	99.94 – 126.74
$AUC_{0-\infty}$ (ng•h/mL)	3328.38 ± 762.94	3220.12	3262.51 ± 936.38	2976.86	108.17	99.01 – 127.25
Treatments						
Test:	Combination product, Batch number LLTSA09001 by Aurobindo Pharma Limited, India					
Reference:	Epivir®, Batch number 6H001 by GSK , USA					
	Viread®, Batch number A171141D by Gilead Sciences Inc., USA					

The 90% confidence intervals for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max} in study 199/09 under fasting conditions. The results for study

200/09 show that the 90% confidence limits for lamivudine are within the 80 to 125% limits. Although the 90% confidence limits for the Cmax of tenofovir are within the 80 to 125%, the 90% confidence limits for AUC of tenofovir are not within the 80 to 125% limits. A probable reason for this is the small sample size. From the clinical point of view an eight percent increase in the exposure does cause safety concerns.

Clinical Site:

Trident Life Sciences Limited
Survey Nos 66 (Part) & 67 (Part)
Miyapur Village, Serilingampally mandal
Hyderabad-500 050, India.

Analytical Site:

APL Research Center
Survey No. 313, Bachupally Village,

Quthubullapur Mandal,
Hyderabad - 500 090, India.

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

Not applicable.

2.2. General Clinical Pharmacology

Not applicable.

2.3. Intrinsic Factors

Not applicable.

2.4. Extrinsic Factors

Not applicable.

2.5. General Biopharmaceutics

2.5.1. What is the in vivo relationship of the proposed formulation to the currently marketed formulation in terms of comparative exposures?

The 90% confidence interval for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max} indicating that the combination tablets are bioequivalent to Viread® plus Epivir®. The results of study 199/09 indicate that the tenofovir disoproxil fumarate / lamivudine 300/300 mg combination tablets provide acceptable exposure compared to the US approved products under fasting conditions.

2.5.2. What is the effect of food on the bioavailability (BA) of tenofovir and lamivudine from the dosage form?

The applicant conducted a fed bioequivalence study. The results of the fed bioequivalence study 200/09 show that the 90% confidence intervals for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max} indicating that the combination tablets are bioequivalent to Viread® plus Epivir®. The results of study 200/09 indicate that the tenofovir/lamivudine 300/300 mg combination tablets provide acceptable exposure compared to the US approved products under fed conditions.

The combined results of the fasted and fed bioequivalence studies indicate that the effect of food on the bioavailability of tenofovir and lamivudine from the combination tablet is similar to the effect observed for the marketed Viread® and Epivir® formulations. Thus, the combination tablet may be administered under fed or fasted conditions, like the innovator products.

2.6. Analytical Section

2.6.1. Pre-Study Bioanalytical Method Validation

The concentrations of tenofovir and lamivudine in human plasma were determined by using liquid chromatography / mass spectrometry / mass spectrometry (LC/MS/MS) methods. Validation of the bioanalytical methods performance used for the determination of concentrations of tenofovir and lamivudine in plasma are presented in the following table.

Table 5: Bioanalytical Method Validation

Analytical Parameters	Tenofovir	Lamivudine
Analytical Range ng/ml	5.00 – 499.87	10.05 – 3998.71
Intra-batch Precision (%CV)	0.96% – 10.88%	1.07% - 8.55%
Intra-batch Accuracy	91.25% - 108.82%	91.09% - 112.13%
Inter-batch Precision (%CV)	3.08% - 9.49%	3.10% - 8.35%
Inter-batch Accuracy	99.61% - 101.89%	95.60% - 102.73%
Recovery	45.43%	49.18%
Freeze-thaw Stability (4 cycles)	96.68% - 102.05%	99.69% - 104.44%
Freezer Stability of Plasma Samples (35 days at -70°C)	104.45% - 106.68%	100.10% - 104.09%

The bioanalytical method is acceptable for the analysis of tenofovir and lamivudine from the plasma samples.

3. LABELING RECOMMENDATIONS

The labeling should indicate that this combination product may be administered without regard to food under fed or fasting conditions.

4. APPENDICES

4.1. Individual Study Reviews

4.1.1. Study 199/09

Title: A randomized, open label, two-treatment, two-sequence, two-period, crossover single-dose comparative oral bioavailability study of fixed dose combination of Lamivudine 300 mg and Tenofovir 300 mg tablets of Aurobindo Pharma Limited, India and Epivir® (lamivudine) 300 mg tablets of GlaxoSmithKline, USA plus Viread® (tenofovir disoproxil fumarate) 300 mg tablets of Gilead Sciences, Inc., USA in healthy adult male subjects, under fasting conditions.

Study Initiation Date: August 7, 2009
Study Completion Date: August 17, 2009

Objective:
To determine the single-dose oral bioavailability of fixed dose combination of lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg tablets of Aurobindo Pharma Limited, India with Epivir® (lamivudine) 300 mg tablets of GlaxoSmithKline, USA plus Viread® (tenofovir disoproxil fumarate) 300 mg tablets of Gilead Sciences, USA in healthy adult male subjects, under fasting conditions.

Study Design:
This was an open-label, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study. Subjects were randomized to receive the following two treatments:

Test treatment:
Combination tablet of 300 mg tenofovir disoproxil fumarate and 300 mg of lamivudine, batch number LTSA09001 by Aurobindo Pharma, India.

Reference treatment:
Epivir® 300 mg of lamivudine tablet, batch number 6H001, GlaxoSmithKline, Research Triangle Park, USA.
Viread® 300 mg of tenofovir disoproxil fumarate tablet, batch number A171141D Gilead Sciences, Inc, USA.

The wash-out period between treatments was 7 days. Subjects received the treatments after an overnight fast of at least 10 hours. Study medications were administered with 240 mL of water.

Study Population Results:
Thirty-five of the thirty-six subjects that were enrolled in this study completed the study. One subject was absent at check-in for the second period. The demographics of the subjects are shown in the following table.

Table 6: Study Subjects

Subject Demographics	
Subjects	All Male
Age (yr)	26.72 ± 6.848 (19 - 45)
Weight (kg)	58.11 ± 6.511 (50 - 69)
Height (cm)	165.53 ± 5.624 (150 - 178)
Race	Asian, Indian
Note: Data presented as mean ± SD (Range)	

Sample Collection for Pharmacokinetic Measurements:
Blood samples (6 mL each) were collected at the following specified times during each period for the determination of concentrations of lamivudine and tenofovir in plasma: prior to dosing (zero hour) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, and 60 hours post dosing.

Bioanalytical Analysis:
A validated bioanalytical method consisting of liquid chromatography with mass spectrometric detection (LC/MS/MS) was utilized in determination of tenofovir and lamivudine in human plasma. The summary of bioanalytical assay performance during analysis of study samples is shown in the following table.

Table 7: Assay Summary

Analytical Parameters	Tenofovir			Lamivudine		
Range ng/mL	5.0 – 496.97			10.14 – 3997.44		
Nominal ng/mL	14.99	209.70	377.84	30.16	1675.35	3035.05
QC Conc. ng/mL	15.05	215.26	391.45	30.83	1665.21	2915.53
Precision (%)	7.15	8.74	23.56	8.04	7.28	11.54
Accuracy (%)	100.40	102.65	103.60	102.21	99.39	96.06

Pharmacokinetic and Statistical Analysis:
WinNonlin version 5.2 was utilized for calculation of the pharmacokinetic parameter values for tenofovir and lamivudine. Table 8 below contains the summary of the pharmacokinetic parameters.

Table 8: Summary of Plasma Pharmacokinetic Parameters

PK Parameters Following Administration of a Single Oral Dose of Tenofovir DF 300 mg and Lamivudine 300 mg under Fasting conditions, Mean ± SD (N=35)		
PK-Parameter	**Test: Combination Product**	**Reference: Viread® + Epivir®**
Lamivudine		
C_{max} (ng/mL)	2133.38 ± 608.53	2194.19 ± 518.92
T_{max} (hr)	2.44 ± 1.08	2.10 ± 1.10
AUC_{0-t} (ng•h/mL)	12714.70 ± 2964.89	12617.46 ± 3050.13
AUC_{inf} (ng•h/mL)	12944.46 ± 3006.37	12853.72 ± 3107.42
$T_{1/2}$ (hr)	11.55 ± 6.59	12.19 ± 7.35
K_{el} $(hr)^{-1}$	0.0775 ± 0.0360	0.0741 ± 0.0375
Tenofovir		
C_{max} (ng/mL)	370.57 ± 121.04	389.76 ± 99.09
T_{max} (hr)	1.26 ± 0.61	1.21 ± 0.58
AUC_{0-t} (ng•h/mL)	2652.34 ± 814.38	2682.19 ± 795.33
AUC_{inf} (ng•h/mL)	2907.02 ± 904.62	2933.79 ± 909.30
$T_{1/2}$ (hr)	18.31 ± 3.82	17.67 ± 3.32
K_{el} $(hr)^{-1}$	0.0395 ± 0.0082	0.0404 ± 0.0070

SAS® software for Windows release 9.1.3 was used for the statistical analysis of this bioequivalence study. The GLM procedure with model being the sequence, subject within the sequence, treatment, and period was used for the analysis of the variance (ANOVA). The statistical analysis for bioequivalence i.e. geometric mean, the point estimate (ratio of test product vs. the reference product), and 90% confidence interval are shown in table 9.

Table 9: Summary statistics

Geometric Mean, Point Estimate, and 90% Confidence Interval for Tenofovir and Lamivudine (N=35)				
PK-Parameter	**Test Product**	**Reference**	**Point Estimate**	**90% CI**
Lamivudine				
Cmax (ng/mL)	2046.23	2131.70	95.99	91.32 – 100.97
AUCt (ng•h/mL)	12353.34	12284.74	100.56	96.01 – 105.34
AUCinf (ng•h/mL)	12579.92	12516.83	100.50	95.98 – 105.21
Tenofovir				
Cmax (ng/mL)	352.19	378.30	93.70	86.03 – 100.92
AUCt (ng•h/mL)	2532.19	2570.63	98.50	94.46 – 102.74
AUCinf (ng•h/mL)	2774.23	2806.79	98.84	94.93 – 102.88

During the review process, the point estimate and 90% confidence intervals were verified. The 90% confidence intervals for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max} indicating that tenofovir DF and lamivudine combination tablets by Aurobindo Pharma Limited are bioequivalent to Viread® and Epivir® under fasted conditions.

Protocol Deviations:
There were numerous delays in the 60-hour blood sample collection in both treatment periods, ranging from 4 - 54 minutes. These deviations are less than 2% of the scheduled time. These protocol deviations do not impact the overall interpretation of study results.

Conclusion:
The 90% confidence intervals for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max}, indicating that tenofovir DF and lamivudine combination tablets by Aurobindo Pharma Limited are bioequivalent to Viread® and Epivir®. The results of study 199/09 indicate that the tenofovir DF / lamivudine 300/300 mg combination tablets provide acceptable exposure compared to Viread® and Epivir® under fasting conditions.

4.1.2. Study 200/09

Title: A randomized, open-label, two-treatment, two-period, two-sequence, crossover, single-dose comparative oral bioavailability study of fixed dose combination of Lamivudine 300 mg and Tenofovir 300 mg tablets of Aurobindo Pharma Limited, India Epivir® (lamivudine) 300 mg tablets of GlaxoSmithKline, USA plus Viread® (tenofovir disoproxil fumarate) 300 mg tablets of Gilead Sciences, Inc., USA in healthy adult male subjects, under fed conditions.

Study Initiation Date: August 7, 2009
Study Completion Date: August 17, 2009

Objective:

To determine the single-dose oral bioavailability of fixed dose combination of lamivudine 300 mg and tenofovir disoproxil fumarate 300 mg tablets of Aurobindo Pharma Limited, India with Epivir® (lamivudine) 300 mg tablets of GlaxoSmithKline, USA plus Viread® (tenofovir disoproxil fumarate) 300 mg tablets of Gilead Sciences, USA in healthy adult male subjects, under fed conditions.

Study Design:

This was an open-label, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study. Subjects were randomized to receive the following two treatments:

Test treatment:
Combination tablet of 300 mg tenofovir disoproxil fumarate and 300 mg of lamivudine, batch number LTSA09001 by Aurobindo Pharma, India.

Reference treatment:
Epivir® 300 mg of lamivudine tablet, batch number 6H001, GlaxoSmith Kline, Research Triangle Park, USA.
Viread® 300 mg of tenofovir disoproxil fumarate tablet, batch number A171141D Gilead Sciences, Inc, USA.

The wash-out period between treatments was 7 days. Subjects received the treatments 30 minutes following the initiation of a high fat breakfast (985 Calorie consisting of 60% fat, 25% carbohydrate and 15% protein) following an overnight fast of at least 10 hours. Study medications were administered with 240 mL of water

Study Population Results:

Thirty-four of the thirty-six subjects that were enrolled in this study completed the study. Two subjects were absent for period two check-in. The demographics of the subjects are shown in the following table.

Table 10: Study Subjects

Subject Demographics	
Subjects	All Male
Age (yr)	26.18 ± 5.52 (19 – 38)
Weight (kg)	58.00 ± 6.13 (50 – 71)
Height (cm)	166.00 ± 5.21 (153 – 174)
BMI (Kg/m^2)	21.07 ± 2.28 (18.17 – 24.86)
Race	Asian, Indian
Note: Data presented as mean ± SD (Range)	

Sample Collection for Pharmacokinetic Measurements:
Blood samples (6 mL each) were collected at the following specified times during each Period for the determination of concentrations of lamivudine and tenofovir in plasma: prior to dosing (zero hour) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, and 60 hours post dosing.

Bioanalytical Analysis:
A validated bioanalytical method consisted of liquid chromatography with mass spectrometric detection (LC/MS/MS) was utilized in determination of tenofovir and lamivudine in human plasma. The summary of assay performance during analysis of study samples is shown in the following table.

Table 11: Assay Summary

Analytical Parameters	Tenofovir			Lamivudine		
Range ng/mL	5.01 – 495.06			10.09 – 3998.08		
Nominal ng/mL	14.99	208.19	375.11	30.25	1680.32	3038.55
QC Conc. ng/mL	14.85	209.20	382.78	30.80	1650.63	2960.11
Precision (%)	8.18	7.35	9.17	8.38	6.41	7.28
Accuracy (%)	99.04	100.48	102.04	101.82	98.23	97.42

Pharmacokinetic and Statistical Analysis:
WinNonlin version 5.2 was utilized for calculation of the pharmacokinetic parameter values for tenofovir and lamivudine. Table 10 below contains the summary of the pharmacokinetic parameters.

Table 12: Summary of Plasma Pharmacokinetic Parameters

PK-Parameters Following Administration of a Single Oral Dose of Tenofovir DF 300 mg and Lamivudine 300 mg under fed conditions, Mean ± SD (N=34)		
PK-Parameter	**Test: Combination Product**	**Reference: Viread®+ Epivir®**
Lamivudine		
C_{max} (ng/mL)	**2112.42 ± 561.91**	**2235.48 ± 547.11**
T_{max} (hr)	**2.14 ± 0.79**	**1.81 ± 0.63**
AUC_{0-t} (ng•h/mL)	**12264.01 ± 2763.25**	**12313.24 ± 2728.83**
AUC_{inf} (ng•h/mL)	**12472.34 ± 2777.68**	**12552.78 ± 2732.99**
$T_{1/2}$ (hr)	**10.59 ± 4.22**	**11.94 ± 7.39**
K_{el} $(hr)^{-1}$	**0.0771 ± 0.0331**	**0.0792 ± 0.0429**
Tenofovir		
C_{max} (ng/mL)	**363.10 ± 110.17**	**380.67 ± 120.59**
T_{max} (hr)	**2.06 ± 0.82**	**1.66 ± 0.66**
AUC_{0-t} (ng•h/mL)	**3031.07 ± 688.01**	**2946.62 ± 818.77**
AUC_{inf} (ng•h/mL)	**3317.08 ± 752.93**	**3233.20 ± 902.99**
$T_{1/2}$ (hr)	**17.23 ± 3.80**	**17.98 ± 6.79**
K_{el} $(hr)^{-1}$	**0.0419 ± 0.0083**	**0.0484 ± 0.0450**

SAS® software for windows release 9.1.3 was used for the statistical analysis of this bioequivalence study. The GLM procedure with model being the sequence, subject within the sequence, treatment, and period was used for the analysis of the variance (ANOVA). The statistical analysis for bioequivalence i.e. geometric mean, the point estimate (ratio of test product vs. the reference product), and 90% confidence interval are shown in table 11.

Table 12: Summary statistics

Geometric Mean, Point Estimate, and 90% Confidence Interval for Tenofovir and Lamivudine (N=34)				
PK-Parameter	**Test Product**	**Reference**	**Point Estimate**	**90% CI**
Lamivudine				
Cmax (ng/mL)	**2033.59**	**2174.17**	**93.53**	**86.68 – 100.89**
AUCt (ng•h/mL)	**11940.67**	**12020.47**	**99.34**	**94.93 – 103.98**
AUCinf (ng•h/mL)	**12155.06**	**12264.66**	**99.11**	**94.93 – 103.46**
Tenofovir				
Cmax (ng/mL)	**346.41**	**356.49**	**97.17**	**88.81 – 106.32**
AUCt (ng•h/mL)	**2931.88**	**2733.13**	**107.27**	**98.52 – 116.80**
AUCinf (ng•h/mL)	**3212.23**	**3000.63**	**107.05**	**98.14 – 116.78**

During the review process, the point estimate and 90% confidence intervals were verified. The values determined during the review process agree with the applicant's values. The 90% confidence interval for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max}, indicating that tenofovir DF and lamivudine tablets by Aurobindo Pharma Limited are bioequivalent to Viread® plus Epivir® under fed conditions.

Protocol Deviations:
There were numerous delays in the 60-hour blood sample collection in both treatment periods, ranging from 4 - 36 minutes. These deviations are less than 2% of the scheduled time. These protocol deviations do not impact the overall interpretation of study results.

Conclusion:
The 90% confidence interval for tenofovir and lamivudine are within 80% - 125% for both AUC and C_{max} indicating that tenofovir DF and lamivudine tablets by Aurobindo Pharma Limited are bioequivalent to Viread® plus Epivir®. The results of study 200/09 indicate that the tenofovir/ lamivudine 300/300 mg combination tablets provide acceptable exposure compared to Viread® and Epivir® under fed conditions.

_____Date:_____
Assadollah Noory, Ph. D.
Clinical Pharmacology Reviewer, DCP 4
Office of Clinical Pharmacology

Concurrence:
_____Date:_____
Kellie Reynolds, Pharm. D.
Deputy Director, DCP 4
Office of Clinical Pharmacology

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ASSADOLLAH NOORY
11/10/2010

KELLIE S REYNOLDS
11/22/2010