CLINICAL PHARMACOLOGY REVIEW

NDA	22-142
Drugs	Efavirenz/Lamivudine/ Tenofovir Disoproxil Fumarate
Formulation; Strength(s)	600 mg /300 mg /300 mg Combination tablet
Indication	Treatment of HIV-1 infection
Applicant	Matrix Laboratories 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
Submission Dates	March 2, 2009; April 17, 2009; May 4, 2009

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1. EXECUTIVE SUMMARY

Matrix Laboratories Limited, India, submitted a New Drug Application under the provisions of 505(b)2 for efavirenz/lamivudine/tenofovir disoproxil fumarate (600 mg /300 mg /300 mg) combination tablet. This application was classified as a priority NDA and it was submitted under the President's Emergency Plan For AIDS Relief (PEPFAR) initiative.

1.1. Recommendation

The clinical pharmacology information provided in this NDA is acceptable. Study 650/08 supports the approval of the combination product Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate 600 mg /300 mg /300 mg tablets by Matrix Laboratories Limited, India.

1.2. Phase IV Commitment

There is no phase IV requirement.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The application for efavirenz/lamivudine/tenofovir df (600 mg /300 mg / 300 mg) combination tablet includes one study report for a bioequivalence study conducted under fasting conditions.

Single-Dose Fasting Bioequivalence Study (650/08)

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

Table 1: Summary Statistics (Study 650/08)

Arithmetic mean +/- SD, Geometric Mean, Point Estimate (T/R), and 90% Confidence Interval						
Parameter	**Test**		**Reference**		**Point Estimate & 90% C. I.**	
	Mean +/- SD	**Geo.Mean**	**Mean +/- SD**	**Geo.Mean**	**P.E.**	**90%CI**
Efavirenz						
Cmax (ng/mL)	2688.89 ± 785.40	2588.04	2894.65 ± 893.18	2746.67	94.22	85.29 – 104.10
AUC_{0-72} (ng•h/mL)*	64849.88 ± 21727.78	61085.67	69724.03 ± 22130.50	66163.65	92.33	85.76 – 99.40
Lamivudine						
Cmax (ng/mL)	2483.33 ± 705.73	2379.21	2582.38 ± 641.29	2504.74	94.99	86.99 – 103.72
AUC_{0-t} (ng•h/mL)	13139.35 ± 3731.15	12574.30	13569.91 ± 3258.13	13155.60	95.58	88.82 – 102.86
$AUC_{0-\infty}$ (ng•h/mL)	13457.37 ± 3716.79	12916.38	13887.73 ± 3228.97	13490.52	95.74	89.28 – 102.67
Tenofovir						
Cmax (ng/mL)	276.83 ± 78.75	265.36	283.09 ± 74.18	266.99	99.39	91.49 – 107.98
AUC_{0-t} (ng•h/mL)	2090.68 ± 575.68	2000.88	2096.06 ± 609.30	1963.50	101.90	92.92 – 111.75
$AUC_{0-\infty}$ (ng•h/mL)	2358.40 ± 627.37	2267.69	2353.08 ± 669.71	2212.08	102.51	94.08 – 111.70
Treatments						
Test	Efavirenz 600 mg, Lamivudine 300 mg, and Tenofovir df 300 mg combination tablet, batch # 1004762, Matrix Laboratories Ltd., India					
Reference	Sustiva® (efavirenz 600 mg) capsules, Batch # 6E22114A, Bristol-Myers Squibb, USA					
	Epivir® (lamivudine 300 mg) tablets, Batch # R245588, GlaxoSmithKline, UK (US approved)					
	Viread® (tenofovir df 300 mg) tablets, Batch # FDB023, Gilead, Sciences Inc., Canada (US approved)					
*- For drugs with long half life partial AUC (AUC_{0-72}) is acceptable						

The 90% confidence limits for both the AUC and C_{max} of efavirenz, lamivudine, and tenofovir are within 80% and 125%, indicating that efavirenz, lamivudine, and tenofovir df combination tablets are bioequivalent to Sustiva®, Epivir®, and Viread® administered together under fasting conditions.

Study Sites:

Clinical Site: Bioserve Clinical Research Pvt. Ltd #6-56/6/1A, Opp. IDPL Factory, Balanagar, Hyderabad-500037 Andhra Pradesh, India	Analytical site: Matrix Laboratories Limited Clinical Research Center, Saradhi Chambers, Plot No. A-4, Beside Poulomi Hospital, Rukminipuri, Dr. A.S. Rao Negar Hyderabad 500 062, India

DSI inspection:

The Division of Scientific Investigation DSI in their memorandum dated April 29, 2009 recommends that the data for study 650/08 be considered acceptable for the agency's review. DSI points out that in the past 2 years these analytical facilities have been inspected three times and that no form 483 was issued and that the personnel of these analytical facilities were highly qualified and took proactive steps to resolve issues.

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 limits for both the AUC and C_{max} of efavirenz, lamivudine, and tenofovir are within 80% and 125% indicating that efavirenz, lamivudine, and tenofovir df combination tablet is bioequivalent to Sustiva®, Epivir®, and Viread® under fasting conditions. Study 650/08 demonstrates that the combination product provides comparable exposure relative to the US approved products.

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

No food effect study or fed bioequivalence study was conducted for this product because the drug label for SUSTIVA® (efavirenz capsules and tablets) recommends that efavirenz not be taken with food because food will increase the exposure of efavirenz which will result in more adverse effects. Therefore, this product must be administered under fasting conditions.

2.6. Analytical Section

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

Table 2: Bioanalytical Method Validation

Analytical Parameters	Efavirenz	Lamivudine	Tenofovir
Analytical Range (ng/ml)	99.88 – 5992.20	24.82 –4001.20	5.00 – 607.88
Lower Quality Control (ng/ml)	99.78	24.82	5.00
Upper Quality Control (ng/ml)	4390.32	2822.26	607.70
Intraday Precision	4.62% - 13.57%	2.52% - 5.31%	2.24% - 5.85%
Intraday Accuracy	92.11% - 107.21%	100.96% - 105.30%	94.89% - 105.75%
Inter day Precision	7.99% - 9.81%	4.07% - 9.33%	4.12% - 8.76%
Inter day Accuracy	96.84% - 102.76%	99.59% - 106.77%	96.63% - 100.98%
Recovery (LQC)	53.25%	95.66%	118.09%*
Recovery (HQC)	55.98%	78.65%	94.29%
Recovery (IS)	41.02%	77.56%	77.56%
Stability			
Bench-top, LQC	-4.46%	-1.07%	-0.39%
Bench-top, HQC	-0.35%	2.82%	1.64%
Freeze-thaw (4 cycles), LQC	2.06%	3.72%	3.98%
Freeze-thaw (4 cycles), HQC	-1.18%	0.46%	0.98%
Long Term Freezer %Change, LQC	(202 days) -1.79%	(279 days) 4.07%	(279 days) 5.56%
Long Term Freezer%Change, HQC	(202 days) -3.19%	(279 days) 4.38%	(279 days) -0.03%
* - Values were for LLQ of QC samples.			

The bioanalytical methods are acceptable for the analysis of efavirenz, lamivudine, and tenofovir from the plasma samples.

3. LABELING RECOMMENDATIONS

In the "DOSAGE AND ADMINISTRATION" section of the label it must indicate that the combination tablet should be administered under fasting conditions as the reference product Sustiva® (efavirenz) is recommended to be administered without food. The labeling for this product adequately reflects the pertinent information regarding all three ingredients used in this product from their respective reference product labels.

4. APPENDIX

4.1. Individual Study Reviews

4.1.1. Study 650/08

Title: A Open Label, Randomized, Two Treatment, Two Period, Two Sequence, Single Dose, Crossover Bioequivalence Study Of Fixed Dose Combination Of Efavirenz 600 mg, Lamivudine 300 mg, Tenofovir df 300 mg Tablets Of Matrix Laboratories Ltd., India Comparing With Respective Reference Formulations Sustiva® 600 mg Capsules of BMS, Epivir® 300 mg Tablets Of GSK, Viread® 300 mg Tablets Of Gilead Sciences, In Healthy Adult Male, Subjects, Under Fasting Conditions.

Dosing Date Period I: September 6, 2008
Dosing Date Period II: October 4, 2008

Objective:

- To assess the bioequivalence of combination tablets containing efavirenz 600 mg + lamivudine 300 mg + tenofovir df 300 mg of Matrix Laboratories Ltd., India and Sustiva® (efavirenz) 600 mg tablets of Bristol-Myers Squibb Company + Epivir® (lamivudine) 300 mg capsules of GlaxoSmithKline + Viread® (tenofovir df) 300 mg tablets of Gilead, Sciences Inc., 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:

Efavirenz 600 mg/lamivudine 300 mg/tenofovir df 300 mg combination tablets, lot number 1004762, expiration April 2010, (Matrix Laboratories Ltd.), India.
Batch size: (b) (4) units.

Reference Treatment:

Sustiva® (efavirenz 600 mg) capsules, batch number 6E22114A, (BMS), USA (US-approved)
Epivir® (lamivudine 300 mg) tablets, batch number R245588, (GSK), UK, (US-approved)
Viread® (tenofovir df 300 mg) tablets, batch number FDB023, (Gilead), Canada (US-approved)
Note: All three reference products were administered together.

Subjects fasted overnight prior to each treatment. Study medications were administered in the fasted state with 240 mL of water. There was a 28-day wash-out period between treatments.

Study Population:
Forty-four of the forty-eight subjects that were enrolled in this study completed the study. Four subjects did not participate in period two of the study (three subjects did not report to the clinical center and one subject had non-compliance alcohol screening). The demographics of the subjects is shown in the following table.

Table 3: Study Subjects

Subjects Demographics	
Subjects	All Male
Age(yr)	27.3 ± 6.6 (18 – 43)
Weight(kg)	60.6 ± 7.0 (50 – 75)
Height(cm)	165.0 ± 5.7 (148 – 175)
Race	Asian (Indian Origin)
Note: Data presented as mean ± SD (Range)	

Formulations:
Reference formulations for this BE study were the US-approved products and the test formulation was manufactured by Matrix Laboratories Ltd., India (please see treatments above).

Sample Collection for Pharmacokinetics Measurements:
Blood samples (6 mL each) were collected at the following specified times during each period for the determination of concentrations of efavirenz, lamivudine, and tenofovir df: prior to dosing (zero hour) and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 36, 48, and 72 hours post dosing.

Bioanalytical Analysis:
A validated bioanalytical method was employed using liquid chromatography with mass spectrometric detection (LC-MS/MS) for determination of efavirenz, lamivudine, and tenofovir in human plasma. The following table shows the bioassay performance for this study.

Table 4: Bioassay Performance

Analytical Parameters	Efavirenz	Lamivudine	Tenofovir
Analytical Range ng/mL	99.50 – 5970.00	24.96 – 3984.94	5.020 – 601.98
Inter-day Precision	6.5% - 7.77%	5.86% - 11.49%	4.47% – 6.64%
Inter-day Accuracy	95.79% - 98.54%	99.63% - 102.55%	95.31% – 95.92%

Pharmacokinetics and Statistical Analysis:
WinNonlin® version 5.0.1 was utilized for calculation of the pharmacokinetics parameter values for efavirenz, lamivudine, and tenofovir. Table 5 contains the summary of the pharmacokinetics parameters.

Table 5: Summary of Plasma Pharmacokinetic Parameters

PK-Parameters for Efavirenz, Lamivudine, and Tenofovir Following Administration of a Single Oral Dose of 600 mg, 300 mg, and 300 mg Respectively, Mean ± SD		
PK-Parameter	**Test: Combination Product**	**Reference:** Sustiva®+Epivir®+Viread®
Efavirenz		
C_{max} (ng/mL)	**2688.89 ± 785.40**	**2894.65 ± 893.18**
T_{max} (hr)	**4.28 ± 1.61**	**3.81 ± 1.18**
$AUC_{(0-72)}$ (ng•h/mL)	**64849.88 ± 21727.78**	**69724.03 ± 22130.50**
$T_{1/2}$ (hr)	**61.48 ± 35.22**	**71.14 ± 83.21**
K_{el} $(hr)^{-1}$	**0.0144 ± 0.0089**	**0.0134 ± 0.0051**
Lamivudine		
C_{max} (ng/mL)	**2483.33 ± 705.73**	**2582.38 ± 641.29**
T_{max} (hr)	**1.92 ± 0.93**	**1.68 ± 0.74**
$AUC_{(0-t)}$ (ng•h/mL)	**13139.35 ± 3731.15**	**13569.91 ± 3258.13**
$AUC_{(0-\infty)}$ (ng•h/mL)	**13457.37 ± 3716.79**	**13887.73 ± 3228.97**
$T_{1/2}$ (hr)	**5.29 ± 1.39**	**4.808 ± 1.14**
K_{el} $(hr)^{-1}$	**0.1425 ± 0.0515**	**0.1542 ± 0.0468**
Tenofovir		
C_{max} (ng/mL)	**276.83 ± 78.75**	**283.09 ± 74.18**
T_{max} (hr)	**1.17 ± 0.57**	**1.12 ± 0.50**
$AUC_{(0-t)}$ (ng•h/mL)	**2090.68 ± 575.68**	**2096.06 ± 609.30**
$AUC_{(0-\infty)}$ (ng•h/mL)	**2358.40 ± 627.37**	**2353.08 ± 669.71**
$T_{1/2}$ (hr)	**18.53 ± 3.57**	**18.08 ± 4.36**
K_{el} $(hr)^{-1}$	**0.0387 ± 0.0070**	**0.0431 ± 0.0286**

The PK-parameters for efavirenz, lamivudine, and tenofovir are similar to the historical values reported in the labels and the literature.
SAS® software for Windows release 9.1.3 was used for the statistical analysis of this bioavailability study. The GLM procedure with model being the subject, subject(seq), treatment, period, and sequence was used for the analysis of the variance. The results of the statistical analysis for bioequivalence i.e. geometric mean, the point estimate (ratio of test product over the reference product), and 90% confidence intervals around the point estimates are shown in the following table.

Table 6: Summary statistic (study 650/08): Geometric Means, Point Estimate, and 90% Confidence Interval for Efavirenz, Lamivudine, and Tenofovir.

Plasma Pharmacokinetics Parameters Following Administration of a Single Oral Dose Under Fasting Conditions in Healthy Subjects				
PK-Parameter	**Test Product**	**Reference**	**Point Estimate (Test/Reference)**	**90% CI**
Efavirenz				
C_{max} (ng/mL)	**2588.04**	**2746.74**	**94.22**	**85.29 – 104.10**
$AUC_{(0-72)}$ (ng•h/mL)	**61085.67**	**66163.65**	**92.33**	**85.76 – 99.40**
Lamivudine				
C_{max} (ng/mL)	**2379.04**	**2504.74**	**94.99**	**86.99 – 103.72**
$AUC_{(0-t)}$ (ng•h/mL)	**12574.30**	**13155.60**	**95.58**	**88.82 – 102.86**
$AUC_{(0-inf)}$ (ng•h/mL)	**12916.38**	**13490.52**	**95.74**	**89.28 – 102.67**
Tenofovir				
C_{max} (ng/mL)	**265.36**	**266.99**	**99.39**	**91.49 – 107.98**
$AUC_{(0-t)}$ (ng•h/mL)	**2000.88**	**1963.50**	**101.90**	**92.92 – 111.75**
$AUC_{(0-inf)}$ (ng•h/mL)	**2267.69**	**2212.08**	**102.51**	**94.08 – 111.70**
Treatments				
Test	Efavirenz 600 mg, Lamivudine 300 mg, and Tenofovir df 300 mg combination tablet, batch # 1004762, Matrix Laboratories Ltd., India			
Reference	Sustiva® (efavirenz 600 mg) capsules, Batch # 7B3070A, Bristol-Myers Squibb, USA (US-approved)			
	Epivir® (lamivudine 300 mg) tablets, Batch # R270680, GlaxoSmithKline, USA (US-approved)			
	Viread® (tenofovir df 300 mg) tablets, Batch # 658080A, Gilead, Sciences Inc., Canada (US-approved)			

During the review process, the point estimates and 90% confidence intervals were verified. The values reported by the applicant were confirmed. The 90% confidence limits for both the AUC and C_{max} of efavirenz, lamivudine, and tenofovir df combination tablet are within 80% and 125%, indicating that efavirenz, lamivudine, and tenofovir df combination tablet is bioequivalent to Sustiva®, Epivir®, and Viread® administered together under fasting conditions.

Protocol Deviations:

There were numerous protocol deviations in blood sample collections due to collapse of vein or cannula blockage at 0.167, 0.667, 6, and 24 hours. These deviations ranged from 3 minutes to 9 minutes. Additional deviations from the protocol include missing blood samples in both periods. These protocol deviations were not considered significant and will not affect the conclusion of the study.

Conclusion:

The 90% confidence interval for lamivudine, efavirenz and tenofovir are within 80% - 125% for both AUC and C_{max}, indicating that efavirenz 600 mg, lamivudine 300 mg, and tenofovir df 300 mg combination tablets are bioequivalent to Sustiva®, Epivir®, and Viread® administered together under fasting conditions.

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Concurrence: _____

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