CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022343Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-343
Drugs	Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate
Formulation; Strength(s)	600 mg /300 mg /300 mg Combination tablet
Indication	Treatment of HIV-1 infection
Applicant	Aurobindo Pharma Limited
Reviewer	Assadollah Noory, Ph.D.
Deputy Division Director	Kellie S. Reynolds, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Submission Dates	May 25, 2012; August 27, 2012

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1. EXECUTIVE SUMMARY

Aurobindo Pharma 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 submitted under the President's Emergency Plan For AIDS Relief (PEPFAR) initiative. The sponsor submitted a bioequivalence study (086-11) in support of the clinical pharmacology requirement for the approval of this NDA. Study 086-11 is a cross-over study assessing the BA/BE of the proposed fixed dose combination to the marketed reference listed products Sustiva®, Epivir®, and Viread®. The information provided by the sponsor adequately addresses the clinical pharmacology requirements from the Office of Clinical Pharmacology perspective.

1.1. Recommendation

The Office of Clinical Pharmacology completed the review of the clinical pharmacology portion of this NDA and finds that the sponsor has adequately addressed the clinical pharmacology aspects required for the approval of this NDA. Therefore, the Office of

Clinical Pharmacology recommends the approval of NDA 22-343. Recommendations for the product label are given on page 6.

1.2. Phase IV Commitment

There is no phase IV requirement.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

This 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 (study 086-11). The study was a randomized, open-label, two-treatment, two-period, two-sequence, single-dose, bioequivalence study. The objective was to assess the bioequivalence between the combination product (efavirenz 600 mg / lamivudine 300 mg /tenofovir df 300 mg) by Aurobindo Pharma Ltd. and Sustiva® (efavirenz 600 mg tablet), Epivir® (lamivudine 300 mg), plus Viread® (tenofovir df 300 mg tablet) in healthy adult subjects. The results from this bioequivalence study are summarized below and the details of the study are included in the individual study review.

Single-Dose Fasting Bioequivalence Study (086-11)

Thirty-seven subjects completed this two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study under fasting conditions. Plasma PK parameter estimates (arithmetic means ± SD and geometric means), point estimates (P.E.) of ratio of test divided by reference expressed as percent, and the 90% confidence intervals (CI) around the 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

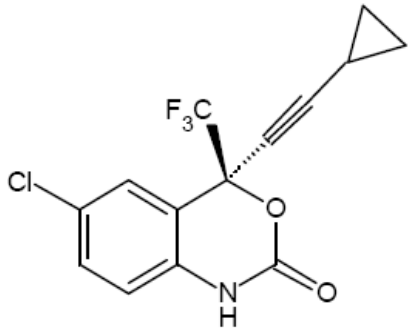
Parameter	Test		Reference		P.E. (%)	90%CI
	Mean ± SD	Geo.Mean	Mean ± SD	Geo.Mean		
Efavirenz						
Cmax (ng/mL)	**3298.09 ± 1217.47**	**3117.96**	**3018.45 ± 1004.36**	**2864.45**	**108.85**	**96.45 – 122.84**
AUC_{0-72} (ng•h/mL)/*	**60968.59 ± 22060.19**	**58014.00**	**59390.50 ± 20355.43**	**56097.06**	**103.42**	**95.47 – 112.03**
Lamivudine						
Cmax (ng/mL)	**2603.95 ± 647.11**	**2512.00**	**2790.12 ± 719.55**	**2687.57**	**93.47**	**85.22 – 102.51**
AUC_{0-t} (ng•h/mL)	**14538.67 ± 3844.31**	**13972.58**	**14638.42 ± 3608.41**	**14126.83**	**98.91**	**92.96 – 105.23**
$AUC_{0-\infty}$ (ng•h/mL)	**14728.66 ± 3839.17**	**14168.89**	**14843.53 ± 3647.63**	**14327.07**	**98.90**	**93.07 – 105.08**
Tenofovir						
Cmax (ng/mL)	**447.07 ± 151.44**	**424.42**	**445.80 ± 169.09**	**418.14**	**101.50**	**95.00 – 108.45**
AUC_{0-t} (ng•h/mL)	**2370.66 ± 574.82**	**2289.90**	**2354.98 ± 705.44**	**2255.64**	**101.52**	**96.14 – 107.19**
$AUC_{0-\infty}$ (ng•h/mL)	**2626.79 ± 585.33**	**2550.60**	**2602.63 ± 732.78**	**2503.57**	**101.88**	**96.80 – 107.22**
Treatments						
Test	Efavirenz 600 mg, Lamivudine 300 mg, and Tenofovir df 300 mg combination tablet, batch # TESA11001, Aurobindo Pharma Ltd., India					
Reference	Sustiva® (efavirenz 600 mg) capsules, Lot # 0B61174A, Bristol-Myers Squibb					
	Epivir® (lamivudine 300 mg) tablets, Lot # 8L001, GlaxoSmithKline					
	Viread® (tenofovir df 300 mg) tablets, Lot # 02006894, Gilead Sciences Inc.					
*- It is acceptable to use partial AUC (AUC_{0-72}) for drugs with long half-life.						

The 90% confidence limits for the (test/reference) ratios of 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.

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

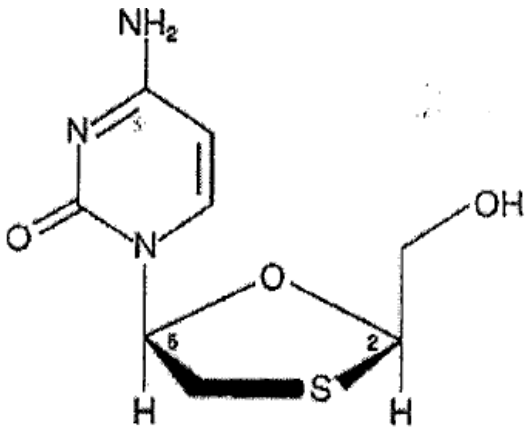
Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). The chemical name of Efavirenz is (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Its empirical formula is $C_{14}H_9ClF_3NO_2$ with a molecular weight of 315.68. Efavirenz is a white to slightly pink crystalline powder and practically insoluble in water.



Structural formula

Efavirenz activity is mediated predominantly by noncompetitive inhibition of HIV-1 reverse transcriptase (RT). HIV-2 RT and human cellular DNA polymerases α, β, γ, and δ are not inhibited by efavirenz.

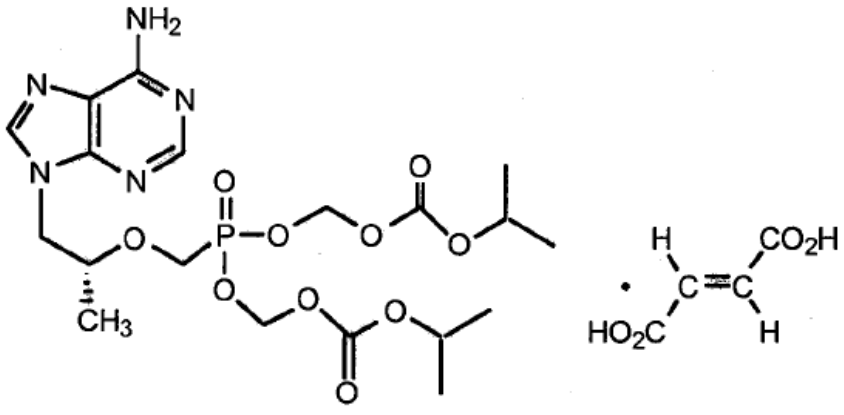
Lamivudine is a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2' ,3'- dideoxy, 3'-thiacytidine. The molecular formula of lamivudine is $C_8H_{11}N_3O_3S$ with a molecular weight of 229.3. Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.



Structural Formula

Lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The principal mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase via DNA chain termination after incorporation of the nucleotide analogue into viral DNA. 3TC-TP is a weak inhibitor of mammalian DNA polymerases α, β, and γ.

Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxy carbonyl oxymethyl ester derivative of tenofovir. Tenofovir disoproxil fumarate is converted to Tenofovir diphosphate, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. The chemical name of tenofovir disoproxil fumarate is 9-((R)-((bis(((isopropoxycarbonyl)oxy) methoxy) phosphinyl)methoxy) propyl) adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_8O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25°C.



Structural formula

Tenofovir diphosphate exhibits activity against HIV-1 reverse transcriptase and HBV polymerase. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and γ.

2.2. General Clinical Pharmacology

Time-to-peak plasma concentration of efavirenz is approximately 3-5 hours and in 6-10 days the steady-state plasma concentrations are reached. Food increases the exposure to efavirenz by 30 to 40 percent based on AUC. The mean cerebrospinal fluid concentration is 0.69% of the corresponding plasma concentration. Efavirenz is highly bound to human plasma proteins, predominantly albumin (99.5-99.75%). It has a terminal half-life of 40-55 hours upon chronic administration. Efavirenz is principally metabolized by the cytochrome P450 system to hydroxylated metabolites; CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism. Efavirenz induces CYP enzymes, resulting in the induction of its own metabolism. Approximately 14-34% of the radiolabel was recovered in the urine and 16-61% was recovered in the feces.

Lamivudine is rapidly absorbed following oral administration, with the absolute bioavailability of approximately 86%. There is no significant difference in systemic exposure in the fed versus the fasted states. Lamivudine distributes into extravascular spaces with an apparent volume of distribution of approximately 1.3 L/kg. The half-life of lamivudine is 5 to 7 hours with the total clearance of approximately 398 mL/min. Over 70% of lamivudine is eliminated unchanged and only 5% is eliminated as trans-sulfoxide.

The oral bioavailability of tenofovir is approximately 25%. Time-to-peak plasma concentration is 1.0 ± 0.4 hour. Food increases the exposure to tenofovir by 40% based on AUC. The protein binding of tenofovir is 7%. In vitro studies indicate that tenofovir is not a substrate of CYP enzymes. The elimination half-life of tenofovir is approximately 17 hours. Following IV administration of tenofovir, approximately 70% to 80% of the dose was recovered in the urine as unchanged tenofovir within 72 hours.

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?

In a randomized, open-label, two-treatment, two-period, two-sequence study the 90% confidence intervals (CI) 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 086-11 demonstrates that the combination product provides comparable exposure relative to the reference 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 or fed bioequivalence study was conducted for this product; because the labeling of Sustiva indicates that it should be taken without food as food increases efavirenz concentrations and may increase the frequency of adverse reactions. Therefore, it is recommended that efavirenz, lamivudine and tenofovir disoproxil fumarate tablets be taken on an empty stomach.

2.6. Bioanalytical

The concentrations of lamivudine and tenofovir in human plasma were determined by using liquid chromatography/mass spectrometry (LC/MS/MS) methods and for determination of the concentrations of efavirenz in human plasma an HPLC-UV method was used. 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)	50.010 - 4994.780	10.010 – 3999.964	5.011 – 608.175
Lower Quality Control (ng/mL)	149.742	30.003	15.013
Upper Quality Control (ng/mL)	3747.300	3050.820	458.116
Intra batch Precision (%)	0.36 to 5.94	1.23 to 6.83	2.15 to 7.98
Intra batch Accuracy (%)	97.41 to 110.05	93.69 to 105.01	96.17 to 107.12
Inter batch Precision (%)	2.81 to 4.27	2.52 to 4.82	4.22 to 6.45
Inter batch Accuracy (%)	102.48 to 106.15	95.09 to 103.53	97.34 to 105.44
Recovery (%)	70.54	49.81	60.96
Stability			
Bench-top, LQC (%)	89.47	101.88	92.69
Bench-top, HQC (%)	107.05	99.45	101.88
Freeze-thaw (4 cycles), LQC (%)	101.47	100.91	101.95
Freeze-thaw (4 cycles), HQC (%)	101.71	98.69	100.52
Freezer Storage LQC (-70°C) %	101.30 (98 Days)	101.82 (203 Days)	96.93 (203 Days)
Freezer Storage HQC (-70°C) %	97.79 (98 Days)	101.69 (203 Days)	94.69 (203 Days)

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 2.1 of the label it must indicate that the combination tablet should be taken on empty stomach, (This information is currently reflected under patient counseling information section (b) (4) .

Regarding the use of this product in pediatrics, the statement under section 8.4 "Pediatric Use" should be reflected in section 2.1 and 17 (b) (4) The labeling for this product adequately reflects the pertinent information regarding all three ingredients used in this product from the respective reference product labeling.

4. INDIVIDUAL STUDY REVIEWS

4.1. Study 086-11

Title:
An open label, randomized, two-treatment, two-sequence, two-period, crossover single-dose comparative oral bioavailability study of fixed dose combination of Efavirenz 600 mg, Lamivudine 300 mg, and Tenofovir disoproxil fumarate 300 mg tablets (Test) of Aurobindo Pharma Ltd, India and respective reference formulations of [SUSTIVA® 600 mg tablets of Bristol-Myers Squibb Company, EPIVIR® 300 mg tablets of GlaxoSmithKline and VIREAD® 300 mg Tablets, of Gilead Sciences, Inc.] USA in 48 healthy, adult, human subjects under fasting conditions

Principal Investigator:

Dr. M. Gyaneshwar
AXIS Clinicals Limited
1-121/1, Miyapur,
Hyderabad – 500 090, India

Start Date: October 02, 2011 Completion Date: November 11, 2011

Objective:

- To assess the bioequivalence of combination tablets containing efavirenz 600 mg + lamivudine 300 mg + tenofovir df 300 mg of Aurobindo Pharma Ltd., India and Sustiva® (efavirenz) 600 mg tablets + Epivir® (lamivudine) 300 mg capsules + Viread® (tenofovir df) 300 mg tablets in healthy adult male subjects, under fasting conditions.
- To monitor the adverse events and to ensure the safety of the subjects.

Study Design:
This was an open-label, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study.

Test treatment:

Efavirenz 600 mg/lamivudine 300 mg/tenofovir df 300 mg combination tablets, lot number TESA11001, expiration June 2013, Batch size: (b) (4). (Aurobindo Pharma Ltd.), India.

Reference Treatment:

Sustiva® (efavirenz 600 mg) capsules, batch number 0B61174A, expiration February 2013, (BMS), USA
Epivir® (lamivudine 300 mg) tablets, batch number 8L001, expiration October 2011 (GSK), USA, Manufactured in Singapore
Viread® (tenofovir df 300 mg) tablets, batch number 02006894, expiration August 2013 (Gilead), USA, Manufactured in Canada
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:
Thirty-seven of the forty-eight subjects that were enrolled in this study completed the study. Eleven subjects dropped out of the study (seven subjects did not report to the clinical center for period two and four subjects withdrew due to vomiting). The demographics of the subjects is shown in the following table.

Table 3: Study Subjects

Subjects Demographics	
Subjects	All Male
Age(yr)	31.58 ± 6.10 (20 – 43)
Weight(kg)	60.58 ± 6.25 (50 – 75)
Height(m)	164.40 ± 6.25 (152 – 175)
BMI (kg/m^2)	22.37 $\pm$ 1.97 (18.56 – 24.96)
Race	Asian (Indian Origin)
Note: Data presented as mean ± SD (Range)	

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: prior to dosing (zero hour) and at 0.25, 0.5, 0.75, 1, 1.25, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 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 concentrations of lamivudine and tenofovir in human plasma and a validated HPLC-UV method was used for determination of concentrations of efavirenz. The following table shows the bioassay performance for this study.

Table 4: Bioassay Performance

Analytical Parameters	Efavirenz			Lamivudine			Tenofovir		
Range	50.04 – 4994.60 ng/mL			10.02 – 3995.98 ng/mL			5.01 – 606.06 ng/mL		
Nominal Con.	149.82	2066.53	3757.32	29.60	1600.04	3091.86	14.99	247.85	459.84
QC Con.	155.87	2150.65	3849.24	30.50	1615.59	3097.97	15.26	248.20	478.74
Precision (%)	4.19	3.98	4.52	5.55	4.46	4.85	6.44	5.20	5.40
Accuracy (%)	104.04	104.07	102.45	103.02	100.97	102.62	101.78	100.14	104.11

Pharmacokinetics and Statistical Analysis:
WinNonlin® version 5.3 was used for calculation of the pharmacokinetics parameters for efavirenz, lamivudine, and tenofovir. The summary of the pharmacokinetics parameters are shown in the following table.

Table 5: **Single Oral Dose of Efavirenz, Lamivudine, and Tenofovir, Mean ± SD, N=37**

PK-Parameter	Test: Combination Product	Ref.: Sustiva®+Epivir®+Viread®
Efavirenz 600 mg		
C_{max} (ng/mL)	3298.09 ± 1217.47	3018.45 ± 1004.36
T_{max} (hr)	3.22 ± 1.29	3.38 ± 1.18
$AUC_{(0-72)}$ (ng•h/mL)*	60968.59 ± 22060.19	59390.50 ± 20355.43
Lamivudine 300 mg		
C_{max} (ng/mL)	2603.95 ± 647.11	2790.12 ± 719.55
T_{max} (hr)	2.47 ± 1.01	1.76 ± 0.85
$AUC_{(0-t)}$ (ng•h/mL)	14538.67 ± 3844.31	14638.42 ± 3608.41
$AUC_{(0-\infty)}$ (ng•h/mL)	14728.66 ± 3839.17	14843.53 ± 3647.63
$T_{1/2}$ (hr)	9.03 ± 4.61	10.60 ± 3.91
K_{el} $(hr)^{-1}$	0.0922 ± 0.0350	0.0741 ± 0.0262
Tenofovir 300 mg		
C_{max} (ng/mL)	447.07 ± 151.44	445.80 ± 169.09
T_{max} (hr)	0.86 ± 0.42	0.86 ± 0.47
$AUC_{(0-t)}$ (ng•h/mL)	2370.66 ± 574.82	2354.98 ± 705.44
$AUC_{(0-\infty)}$ (ng•h/mL)	2626.79 ± 585.33	2602.63 ± 732.78
$T_{1/2}$ (hr)	20.07 ± 4.34	20.22 ± 4.11
K_{el} $(hr)^{-1}$	0.0356 ± 0.0057	0.0355 ± 0.0064
*- It is acceptable to use partial AUC (AUC_{0-72}) for drugs with long half-life.		

The PK-parameters for efavirenz, lamivudine, and tenofovir are similar to the historical values.

SAS® software for Windows release 9.1.3 was used for the statistical analysis of this bioavailability study. The GLM procedure with model being sequence, subject(seq), treatment, and period was used for the analysis of the variance. The results of the statistical analysis for bioequivalence, i.e. geometric means, point estimates (PE) as ratio of test divided by reference expressed as percent, and 90% confidence intervals (CI) are shown in the following table.

Table 6: Summary Statistics

PK-Parameter	Test, Geo-Mean	Ref., Geo-Mean	Point Estimate T/R, %	90% CI
Efavirenz				
C_{max} (ng/mL)	**3117.96**	**2864.45**	**108.85**	**96.45 – 122.84**
$AUC_{(0-72)}$ (ng•h/mL)*	**58014**	**56097.06**	**103.42**	**95.47 – 112.03**
Lamivudine				
C_{max} (ng/mL)	**2512.00**	**2687.57**	**93.47**	**85.22 – 102.51**
$AUC_{(0-t)}$ (ng•h/mL)	**13972.58**	**14126.83**	**98.91**	**92.96 – 105.23**
$AUC_{(0-inf)}$ (ng•h/mL)	**14168.89**	**14327.07**	**98.90**	**93.07 – 105.08**
Tenofovir				
C_{max} (ng/mL)	**424.42**	**418.14**	**101.50**	**95.00 – 108.45**
$AUC_{(0-t)}$ (ng•h/mL)	**2289.90**	**2255.64**	**101.52**	**96.14 – 107.19**
$AUC_{(0-inf)}$ (ng•h/mL)	**2550.60**	**2503.57**	**101.88**	**96.80 – 107.22**
*- It is acceptable to use partial AUC (AUC_{0-72}) for drugs with long half-life.				

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 the (test/reference) ratios of 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® administered together under fasting conditions.

Safety and Tolerability:
There were no serious adverse events. There were one moderate (increased SGPT) and ten mild (dizziness, vomiting) adverse events reported during the study. The test and reference products were tolerated well by the study subjects.

Protocol Deviations:
There were numerous protocol deviations in blood sample collections at 2.5 and 72 hours. These deviations ranged from 8 minutes (5.3%) to 72 minutes (1.7%) from the scheduled time points. These protocol deviations were not considered significant and will not affect the conclusion of the study.

Conclusion:
The 90% confidence intervals for efavirenz, lamivudine, and tenofovir are within 80% and 125% for the (test/reference) ratios of the 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.

Office of Scientific Investigation inspection:
The Division of Bioequivalence and GLP compliance in OSI recommends that the data for study 086-11 are acceptable for the agency's review. The OSI memorandum was completed on November 9, 2012.

Study Sites:

Clinical Site:
AXIS Clinicals Limited
1-121/1, Miyapur,
Hyderabad – 500 090, India

Analytical site:
Aurobindo Pharma Limited
Survey No. 313, Bachupally Village,
Quthubullapur Mandal,
Hyderabad – 500 090, India

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
11/14/2012

KELLIE S REYNOLDS
11/15/2012