# NDA 208255 CLINICAL PHARMACOLOGY REVIEW

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| **NDA** | 208255 |
| **Submission Type** | 505(b)(2) |
| **Submission Date** | 09/13/2016 |
| **Generic Name** | Efavirenz (EFV), Lamivudine (3TC), Tenofovir DF (TDF) |
| **Brand Name** | N/A |
| **Indication** | Treatment of HIV |
| **Dosage Form/ Strength** | Tablet: EFV (400 mg) / 3TC (300 mg) / TDF(300 mg) |
| **Applicant** | Mylan |
| **Review Team** | Islam R. Younis, Ph.D. |

**Background**

This 505(b)(2) application was submitted under the provisions of the President's Emergency Plan for AIDS Relief (PEPFAR). The applicant developed a fixed dose combination (FDC) tablet containing EFV, 3TC, and TDF. This is the first application to seek approval for an HIV regimen containing 400 mg EFV. The currently approved EFV therapeutic dose is 600 mg.

**Basis for Approval**

The applicant obtained right of reference to ENCORE1 clinical trial which established the efficacy and safety of the 400 mg dose of EFV. ENCORE1 was randomized, double-blind, active-controlled, two-arm, parallel groups multinational clinical trial which evaluated the safety and efficacy of EVF 400 mg dose relative to EVF 600 mg dose. In both treatment arms EFV was administered once daily in combination with Truvada®, a FDC of emtricitabine (FTC, 200 mg) and TDF (300 mg). The proportion of patients with a viral load < 200 copies/mL in the mITT analysis was 302/321 (94.08%) in the EFV 400 mg treatment arm and 285/309 (92.23%) in the EFV 600 mg treatment arm (difference 1.85, 95% CI −2·1 to 5.79).

The applicant conducted a relative bioavailability study (Study C15275) to compare the exposures of EFV, 3TC, and TDF following the administration of the FDC tablet and the individual EFV (Efamat 200 mg), 3TC (Epivir® 300 mg), and TDF (Viread® 300 mg) agents administered in combination. This study bridges efficacy and safety information from ENCORE1 to the FDC tablet because Efamat is the EFV formulation used in ENCROE1. The exposure of EFV, 3TC, and TDF were similar following the administration of the FDC relative to the individual agents (Table 1).

| Drug | Parameter | Geometric Mean Ratio (90% CI) |
|---|---|---|
| Efavirenz | $AUC_{0-72}$ | 0.96 (0.92,1.0) |
| | Cmax | 0.92(0.85,0.99) |
| Lamivudine | AUC | 1.04 (0.99,1.08) |
| | Cmax | 0.89(0.83,0.96) |
| Tenofovir | AUC | 1.03(0.98,1.07) |
| | Cmax | 0.96(0.90,1.02) |

**Recommendations**

The application is recommended for approval from clinical pharmacology perspective. The indication can be extended to pediatrics 12 years of age and older and weighing at least 35 Kg. The pharmacokinetics of EFV is linear in the dose range 200 to 600 mg; therefore the administration of EFV 400 mg dose is expected to produce exposure in adolescents similar to those observed in adults in similar manner to what was observed with EFV 600 mg dose. The efficacy of the 400 mg dose of EFV was shown to be non-

inferior to EFV 600 mg dose in adults. Safety of EFV 600 mg dose in adolescents has been established and therefore there is no need to obtain additional safety information for EFV 400 mg dose in adolescents.

**Labeling Recommendations**

Labeling negotiations were ongoing at the time of this review.

# Appendix Individual Study Review

| Relative Bioavailability Study | | | | |
|---|---|---|---|---|
| **Study #** | C15275 | **Study Period** | 11/20/2015-12/23/2015 | **EDR Link** |
| **Title** | A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Test product Tenofovir disoproxil fumarate, Lamivudine and Efavirenz film-coated tablets 300 mg / 300 mg/ 400 mg of Mylan Laboratories Limited, India with Reference product (R= R1 + R2 + R3) (R1: VIREAD® Tablets (Tenofovir disoproxil fumarate) 300 mg manufactured and distributed by Gilead Sciences, Inc. Foster City, CA 94404, R2: EPIVIR® Tablets (Lamivudine) 300 mg Manufactured by GlaxoSmithKline Research Triangle Park, NC 27709, R3: Two tablets of Efamat (Efavirenz) 200 mg manufactured by Mylan Laboratories Ltd, India), in normal healthy adult human subjects under fasting conditions. | | | |

**STUDY DESIGN**

Randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover study. Washout period was 24 days.

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| Population | ☑ Healthy Volunteers ☐ Patients |
| Study Rationale | To evaluate the relative bioavailability of EFV, 3TC, and TDF following the administration of film-coated fixed dose combination (Mylan FDC) relative to the individual agents administered in combination |
| Treatments | See table below |
| Dose Selection Rationale | EFV dose is the dose evaluated in ENCORE1 clinical efficacy and safety trial. 3TC and TDF doses are the approved therapeutic doses and the reference listed formulation was used in the study |
| Administration | ☑ Fasted ☐ Fed |
| Interfering Substances Excluded | Caffeine and xanthine-containing foods or beverages (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas,etc.), any Grapefruit juice or related products, tobacco containing products. |
| Sampling Times | Pre-dose, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 24, 36, 48,and 72 hours post-dose. |
| PK Parameters | Primary: AUCt ($AUC_{0-72}$ for EFV), $C_{max}$<br>Secondary: $T_{max}$, $t_{1/2}$, $K_{el}$ (All) $AUC_{0-inf}$ and $AUC_{0-t}$ / $AUC_{0-inf}$ *100 ( |
| PK Analysis | Non-compartment analysis using linear trapezoidal method |
| Statistical Analysis | ANOVA including sequence, formulation and period as fixed effects and subject (sequence) as a random effect. Sequence effect was tested using subject (sequence) as an error term. |

| Arm | API( Trade Name) | Batch No., Expiry date |
|---|---|---|
| Test | EVF, 3TC, TDF (FDC Tablet) | 2009057/ April 2017 |
| Reference | TDF 300 mg(Viread®) | 002181/July 2018 |
| | 3TC 300 mg (Epivir®) | 3ZP8520/July 2016 |
| | EFV 200 mg (Efamat): 2 tablets | 8036093/March 2018 |

Is the study design acceptable? ☑ Yes ☐ No

**STUDY CONDUCT**

**Bioanalytical Method:**

| Analyte | EFV | 3TC | Tenfovir |
|---|---|---|---|
| Method Type | LC/MS-MS | LC/MS-MS | LC/MS-MS |
| Range | 100-4000 ng/mL(revised LLOQ to 50 ng/mL) | 5 – 600 ng/mL | 24 – 400 ng/mL |
| Matrix | Plasma | Plasma | Plasma |

| | | |
|---|---|---|
| Validation | ▪ Method validated prior to use | ☑ Yes ☐ No ☐ NA |

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| | ▪ Method validation acceptable | ☑ Yes ☐ No ☐ NA |
| Study Samples Analysis | ▪ Samples analyzed within the established stability period<br>▪ Quality control samples range acceptable<br>▪ Chromatograms provided<br>▪ Accuracy and precision of the calibration curve acceptable<br>▪ Accuracy and precision of the quality control samples acceptable<br>▪ Incurred samples analysis is acceptable<br>▪ Overall performance acceptable | ☑ Yes ☐ No<br>☑ Yes ☐ No<br>☑ Yes ☐ No<br>☑ Yes ☐ No<br>☑ Yes ☐ No<br>☑ Yes ☐ No<br>☑ Yes ☐ No |
| Inspection | ▪ Will the bioanalytical site be inspected | ☑ Yes ☐ No |

**Protocol Deviations**

- Are there any protocol deviations listed in the study report? ☑ Yes ☐ No
- Do any of the listed deviations affect the integrity of the study? ☐ Yes ☑ No ☐ NA

**Notes:**

*For some subjects, plasma samples in period I and Period II were collected beyond the scheduled sampling time. There was no impact on the study outcome as actual time points of sample collection was used for pharmacokinetic analysis.*

## STUDY RESULTS

**Study Population**

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| Enrolled<br>Treated<br>Completed<br>Discontinued Due to AE<br>PK Population/Safety Population | 76<br>70<br>64<br>1<br>64 (62 for EFV)/65 |
| Age [Mean (SD)] | 32 (5.8) |
| Male/Female | Not Available |
| Race (Caucasian/Black/Asian/Hispanic) | Indian Asian (All) |

**Pharmacokinetics (**Geometric Mean Ratio & 90% CI)

| Drug | Parameter | GMR (90% CI) |
|---|---|---|
| Efavirenz | $AUC_{0-72}$ | 0.96 (0.92,1.0) |
| | Cmax | 0.91 0.85,0.99) |
| Lamivudine | AUC | 1.04 (0.99,1.08) |
| | Cmax | 0.89 0.83,0.96) |
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| | Cmax | 0.96 0.90,1.02) |

- Were there any outliers or excluded data from analysis? ☑ Yes ☐ No ☐ NA

*Subjects 27 and 71 were excluded from pharmacokinetic and statistical data analysis of EFV as these subjects have predose concentrations of EFV for both periods greater than 5% of Cmax. The exclusion of these subjects does not affect trial outcome because the trial had sufficient power (post hoc estimate of ~ 100%) to evaluate similarity in exposure. Including these subjects in the analysis did not change study outcomes.*

- Are the study results acceptable? ☑ Yes ☐ No

**Safety**

Was there any death or serious adverse events? ☐ Yes ☑ No

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ISLAM R YOUNIS
02/17/2017