# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**202123Orig1s000**

# SUMMARY REVIEW

# CROSS DISCIPLINE TEAM LEADER REVIEW

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| **Date** | July 19, 2011 |
| **From** | Sarah Robertson, Pharm.D. |
| **Subject** | Cross Discipline Team Leader Review |
| **NDA #** | 202-123 |
| **Applicant** | Gilead Sciences Inc. |
| **Date of Submission** | February 10, 2011 |
| **PDUFA Goal Date** | August 10, 2011 |
| **Proprietary Name / Established (USAN) names** | Complera (Emtricitabine/Rilpivirine/Tenofovir DF Fixed-Dose Combination) |
| **Dosage forms / Strength** | 200 mg / 25 mg / 300 mg (FTC/RPV/TDF) |
| **Approved Indication(s)** | A complete regimen for the treatment of HIV-1 infection in treatment-naïve adult patients |
| **Recommended:** | Approval, pending a recommendation from the Office of Compliance regarding the acceptability of the remaining manufacturing site inspections. |

## 1. Introduction

This review summarizes the multi-disciplinary evaluation of the information submitted by Gilead in NDA 202-123 to support approval of a fixed-dose combination (FDC) tablet containing rilpivirine, an NNRTI, with emtricitabine and tenofovir, two NRTIs. Rilpivirine (EDURANT) was recently approved (May 2011) under NDA 202-022 for the treatment of HIV-1 infection in treatment naïve adult patients. Thus, the FDC tablet proposed in this NDA will be approved as a complete regimen only for treatment-naïve adults. No new clinical safety or efficacy trials were submitted with the current NDA. Cross reference was made to the clinical trials conducted by Tibotec in support of the rilpivirine NDA (TMC278-C209 and TMC278-C215). Gilead submitted the results of two BA/BE studies evaluating the proposed commercial FDC tablet relative to the individually administered agents in healthy subjects, including one study conducted under fed conditions (GS-US-264-103) and one study conducted under fasted conditions (GS-US-264-108).

To obtain regulatory approval, the data submitted must provide evidence that the proposed FDC tablet will provide the same exposure for each of the three drugs as the individually administered approved agents, when administered as directed.

## 2. CMC/Biopharmaceutics

I agree with the conclusions of the CMC reviewer, Dr. Rao Kambhampati and the biopharmaceutics reviewer, Dr. Elsbeth Chikhale. Dr. Kambhampat concluded that the Applicant provided sufficient information to ensure the identity, strength, purity and quality of the drug product. However, a recommendation regarding the overall acceptability of the manufacturing facilities could not be provided at the time the CMC review was finalized, as the results of one manufacturing site inspection by the Office of Compliance was outstanding. At the time of finalization of this CDTL memo, the (b) (4) emtricitabine drug substance manufacturing site is still outstanding.

Dr. Chikhale reviewed the proposed dissolution method for the FDC tablet and found the method acceptable. However, the Applicant did not agree with the revised dissolution acceptance criteria proposed by Dr. Chikhale. Agreement was made that the Applicant's originally proposed acceptance criteria would be used on an interim basis. Gilead has agreed to a PMC to collect additional dissolution data from their full-scale batches in order to set the final regulatory dissolution specifications. I agree with the PMC proposed by Dr. Chikhale.

*Drug Product*

Complera FDC tablet contains 200 mg of emtricitabine, 25 mg of rilpivirine (27.5 mg rilpivirine HCl) and 300 mg tenofovir disoproxil fumarate. The tablets are capsule shaped, film-coated, purplish-pink, and debossed with "GSI" on one side and plain faced on the other side. (b) (4) The tablets are packaged in 30 count white, high density polyethylene (HDPE) bottles. Each tablet contains the following inactive ingredients: (b) (4) microcrystalline cellulose, (b) (4) lactose monohydrate, (b) (4) povidone, (b) (4) pregelatinized starch, (b) (4) Polysorbate 20, (b) (4) Croscarmellose Sodium, and (b) (4) (b) (4) magnesium stearate. The tablets are coated with (b) (4) film coat that is made of hypromellose,

(b) (4) (FS&C Blue #2) aluminum lake, lactose monohydrate, poly ethyleneglycol, red iron oxide, (b) (4) (b) (4) (FD&C Yellow #6) aluminum lake, titanium dioxide, and triacetin. All the excipients are of compendial grade except the colorant which complies with federal food regulations. (b) (4)

The drug product tablets are manufactured by (b) (4) The proposed commercial batch size for manufacture is (b) (4) The manufacturing process includes (b) (4) (b) (4) (b) (4) In-process testing is appropriately applied during the manufacturing process. The critical steps of the process are controlled via equipment operating parameters and testing during the process. The critical process steps and process tests for the identified steps were provided. The manufacturing procedure for the clinical bioequivalence and the proposed commercial formulation were demonstrated to be robust by the successful manufacture of representative batches (b) (4) These scale-up experiences led to the final commercial manufacturing process of the selected formulation. Process validation will be completed (b) (4) (b) (4) and include an expanded sampling plan to demonstrate consistent product quality throughout the unit process steps during the manufacture of each batch. Process validation will be performed prior to commercial distribution of Complera tablets. All excipients used in the manufacture of the tablets meet USP/NF and Ph. Eur. standards, except for the film-coating material which is tested according to an in-house standard. (b) (4)

The specifications for the tablets included appearance, identification by chromatographic retention time, identification by UV spectroscopy, (b) (4), strength, degradation product content, uniformity of dosage units, and dissolution. The initial submission did not contain acceptance criteria for (b) (4) (b) (4) degradants in the shelf-life specification, but they were included in the resubmission. On the basis of the batch release, stability data, and statistical analysis of the stability data and comparative stability of the proposed tablets with Truvada and Edurant tablets, the Applicant was advised to tighten many of the shelf-life acceptance criteria for the degradation products; the Applicant (b) (4) many of the acceptance criteria and provided adequate justification for the others. A description was provided for all the analytical methods and the validation reports were provided for the identity of tablets by UV, identity, strength, and degradation products content of tablets by HPLC, content uniformity, and dissolution method. A justification was provided for not including the microbial limits test in the drug product specification on the basis of the microbial test results of the three stability lots at release and at 12 month long-term stability test point. The batch analysis results were provided for six batches, which included pivotal clinical, primary stability, and scale-up lots. The results demonstrated that the tablets can be manufactured with consistent quality and purity. The stability data were provided for three registration lots. The data included 12 months long-term (25°C/60%RH and 30°C/75% RH) and 6 months accelerated (40°C/75%RH) stability and comparison of the results with those of Atripla and Truvada tablets. On the basis of this information, the Applicant suggested an expiration dating period of 24 months when the tablets are stored at 25°C for the US and stored below 30°C (b) (4). This is acceptable to the CMC reviewer.

*Drug Substance*

All three APIs were previously approved by the FDA for their use in single ingredient drug products (Emtriva Capsules, Emtriva Oral Solution, Edurant Tablets, and Viread Tablets) and fixed dose combination tablets (Truvada Tablets and Atripla Tablets). The CMC information for drug substances was cross-referenced to Gilead's approved NDA 21-752 for emtricitabine drug substance information, (b) (4) DMF (b) (4) for RPV HCl drug substance information, and Gilead's approved NDA 21-356 for TDF drug substance information. The DMF (b) (4) was recently reviewed by Maotang Zhou (ONDQA) and it was found to be adequate. In addition, the Applicant provided some additional information in the submission, including nomenclature, structure, general properties, manufacturers, and specification. However, the batch analysis information was not provided in the initial submission (9/3/10). Upon request (6/2/11), certificates of analysis were provided for 7 lots of emtricitabine, 5 lots of TDF, and 6 lots of RPV HCl. These lots included results of emtricitabine manufactured at (b) (4) TDF manufactured at (b) (4) ( (b) (4) (b) (4) and RPV HCl manufactured at (b) (4) (b) (4) These lots were used for the manufacturing of the stability, clinical, and/or scale-up drug product tablet lots. The emtricitabine drug substance batches that were stored for 16 to 41 months were analyzed for the presence of (b) (4) impurities and none of the lots contained any detectable level of these

impurities. Thus, the Applicant has successfully demonstrated that [redacted] (b) (4) are not formed in the drug substance at release and during storage. The proposed specifications for all three APIs are same as those approved previously for other NDAs.

*Dissolution*
The proposed dissolution method (Apparatus 2, 75 rpm, dissolution medium 1000 mL of 0.5% polysorbate 20 in 0.01N HCl, pH 2.0, at 37°C) is sufficient for demonstrating the ability to show differences in manufacturing process parameters that have the potential to impact dissolution, including RPV drug substance particle size, [redacted] (b) (4) and presence of tablet coating. The dissolution method was found acceptable by Dr. Chikhale. However, based on her review of the dissolution data provided, Dr. Chikhale proposed the following alternative acceptance criteria: Q= (b) (4) at 20 minutes for FTC and TDF and Q= (b) (4) at 60 minutes for RPV. Upon further discussion with the Applicant, the following criteria were agreed upon to be used on an interim basis until further data are available: Q= (b) (4) at 30 minutes for FTC and TDF and Q= (b) (4) at 60 minutes for (b) (4) The Applicant agreed to a PMC to collect additional dissolution data from full-scale batches before setting the final regulatory dissolution specifications. Specifically, the Applicant agreed to collect dissolution profile data from all the full-scale batches manufactured during the first year following approval. The collected dissolution data will target the FDA's recommended specifications (as outlined above) with dissolution testing at Stage 1, 2, or 3 as appropriate.

The Applicant attempted to develop an in vivo-in vitro correlation (IVIVC). Experiments were conducted to evaluate BCS Class 2 compound RPV in the FDC tablet; results showed that the dissolution criteria explored lacked the discriminating power necessary to support an IVIVC. Therefore, further attempts at developing an IVIVC were not pursued further.

Dr. Chikhale has concluded the access program tablets can be considered equivalent based on comparative release and stability dissolution data.

### 3. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with this NDA; all nonclinical information is cross-referenced to the original NDAs for the individual entities.

### 4. Clinical Pharmacology

I agree with the summary and conclusions as outlined in the clinical pharmacology review by Dr. Stanley Au. As summarized in his review, RPV is currently labeled to be administered with meals, while TDF and FTC may be administered without regard to food. In Study 103 the proposed commercial FDC was compared in a 3-way crossover BA/BE study with another test formulation and the individual reference formulations for RPV, TDF and FTC under fed conditions (standardized breakfast containing 400 kcal and 13 g fat). The results of the statistical analyses showed the 90% CIs for Cmax, $AUC_{0\text{-last}}$ and $AUC_{inf}$ all fell within the bioequivalency limits of 80-125% for each of the three components; thus, the proposed commercial formulation is bioequivalent to the individual reference formulations under fed conditions. Since Study 103 was considered pivotal to the approval of the proposed FDC tablet, a consult was sent to the Office of Scientific Investigation to inspect the bioanalytical laboratories that analyzed the three analytes in plasma [redacted] (b) (4) as well as the clinical study site (SeaView Research). The inspections at (b) (4) and SeaView Research did not reveal any significant findings and no form FDA-483 was issued to either site. Form FDA-483 was issued to [redacted] (b) (4) with five observations. One of the 483 observations was a lack of sufficient long-term storage stability data when FTC, tenofovir (TFV) and RPV were combined in the same matrix. To address this deficiency, additional long-term stability studies were conducted and found acceptable. All of the remaining 483 observations were sufficiently addressed by (b) (4) to the satisfaction of OSI, and the clinical and bioanalytical data were found acceptable for review. Please see reviews by Dr. Stanley Au and Dr. Gopa Biswas (DBGC, OSI) for further details regarding inspection issues.

A second BA/BE study was conducted in healthy volunteers to compare the commercial FDC tablet to the individual reference formulations under fasted conditions (Study 108). The study results indicate the FDC tablet is not bioequivalent to the individual components under fasted conditions; the upper bound of the 90% CI for TFV and RPV parameters exceeded 125%, while FTC was bioequivalent. RPV Cmax and AUC were approximately 25% higher with the FDC tablet relative to the individual reference tablet under fasted conditions. Thus, the effect of food on RPV absorption appears to be attenuated with the FDC relative to the individual EDURANT tablet. RPV exposure is 40% lower when EDURANT is given fasted relative to administration with a

standard meal or a high-fat, high-calorie meal. The proposed FDC tablet will be labeled to be administered with food, consistent with approved labeling for the RPV tablet.

**5. Clinical Microbiology**

I concur with the summary of results and conclusions as outlined in the microbiology review of Dr. Lisa Naeger. As outlined in Dr. Naeger's review, nonclinical virology studies were conducted to assess the antiviral activity and resistance of the triple combination of FTC + RPV + TFV in vitro. The combination was evaluated in a 5-day cytophathic assay in MT-2 cells infected with HIV-1. The triple combination showed moderate synergy and no evidence of antagonistic interaction among the drugs in 2 or 3 drug combinations. Dose escalation and fixed-dose breakthrough selection experiments were performed in HIV-1 infected MT-2 cells. The combination resulted in the M184I reverse transcriptase (RT) substitution by Day 47, with no additional substitutions detected at Days 57 or 74. The fixed-dose breakthrough experiments, which evaluated the selective pressure of the drugs in a fixed 1:1:1 ratio based on their respective EC50 values, showed the combination resulted in the M184I RT substitution in the 1.7x:1.7x:1.7x EC50 drug culture and the K65R substitution in the 3.3x:3.3x:3.3x EC50 culture. In cross-resistance experiments assessing the susceptibility of FTC, TFV and RPV to wild-type and 141 mutant HIV-1 viruses, the data showed that viruses containing NNRTI mutations that lack M184V/I are not cross-resistant to FTC, and viruses containing NNRTI substitutions are not cross-resistant to TFV. Overall, the results demonstrated a lack of cross-resistance of HIV-1 with RPV-resistance-associated substitutions and other NNRTI resistance-associated substitutions to FTC and TFV.

In addition to the review of nonclinical virology data, Dr. Naeger recommended changes to the proposed language in the Microbiology section of the label based on her review of the virologic failures among subjects receiving FTC/TDF in clinical trials C209 and C215. I agree with the revisions recommended by Dr. Naeger.

**6. Clinical/Statistical- Efficacy**

No clinical efficacy trials were conducted with the FDC product. The efficacy of RPV was established based on clinical trials C209 and C215, which compared RPV to efavirenz (EFV) in treatment-naïve patients when given in combination with background regimen TDF/FTC (C209) or TDF/FTC, zidovudine/lamivudine or abacavir/lamivudine (C215). The two Phase 3 trials were identical in design with the exception of the choice of background regimen. The medical officer, Dr. Yodit Belew, focused her review on the efficacy results for the subjects in C209 and C215 that received FTC/TDF as the background regimen. I agree with the conclusions of Dr. Belew, who reviewed the efficacy data jointly with the statistics reviewer, Dr. Frasier Smith. In brief, a snapshot analysis of the primary efficacy variable (proportion of subjects with viral load < 50 copies/mL at 48 weeks) was conducted to assess the non-inferiority of RPV versus the control using combined data from all subjects receiving FTC/TDF in the two trials. The analysis demonstrated non-inferiority of RPV vs. control with regard to the primary efficacy parameter with a pre-defined non-inferiority margin of 12%. The proportion of virologic response at week 48 was 83% for RPV and 81% for the EFV group. However, compared to the EFV treatment group, virologic failure rates were significantly higher in RPV subjects for the subgroup of subjects with baseline viral load > 100,000 copies/mL (p=0.004). This finding is consistent with what was seen in the overall population enrolled in C209 and C215. More subjects discontinued RPV for virologic failure, while more subjects discontinued EFV due to adverse events. Similar to the approved label for EDURANT, the proposed label for the FDC tablet will state the following considerations for use under Indications and Usage:

- More EDURANT treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure compared to subjects with HIV-1 RNA less than 100,000 copies/mL at the start of therapy.
- The observed virologic failure rate in EDURANT treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz.
- More subjects treated with EDURANT developed lamivudine/emtricitabine associated resistance compared to efavirenz.

**7. Safety**

The primary focus of Dr. Belew's clinical safety review focused on RPV, since it was just recently approved in May 2011, while TDF and FTC have been approved for several years and the safety profile of each agent is well characterized. Dr. Belew's review focuses primarily on the safety findings from subjects who received FTC/TDF

in C209 and C215. I agree with the Dr. Belew's conclusions that the safety profile of the FDC product reflects the individual components, and new safety signals are expected.

Among patients receiving FTC/TDF, discontinuation due to AEs was higher in the EFV group than the RPV group (8% vs. 3%), similar to the overall study population. The most common AE leading to discontinuation was psychiatric disorders (1% in RPV and 2% in EFV). The most common SAE was infection/infestation (2% in each group). Serious hepatobilliary disorders and renal disorders were reported more frequently in the RPV group compared to the EFV group. Five RPV treated subjects experienced a hepatobiliary event compared to one EFV treated subject. Among subjects treated with FTC/TDF, the majority of adverse events were grade 1 or 2 in severity. Similar proportions of subjects receiving FTC/TDF experienced at least 1 AE during treatment with RPV (90%) or efavirenz (92%). The most commonly reported adverse events (all cause, all severity) with RPV were headache (14%), diarrhea (13%), nausea (12%) and nasopharyngitis (12%).

Based on the preclinical profile and known toxicities for the NNRTI drug class, the safety evaluation for RPV included rash, neuropsychiatric disorders, hepatobiliary disorders, renal disorders, adrenal disorders and cardiac events. RPV had less rash compared to EFV (13% vs. 25% for all cause, all severity; 2% vs. 9% for ≥ grade 2 and treatment related). All rash events were reported with similar incidence in the overall population regardless of background regimen. More subjects treated with EFV developed a neurologic event (all cause, all severity) compared to RPV (47% vs. 31%). Psychiatric events (all cause, all severity) were reported in 25% for RPV and 32% of efavirenz treated subjects. The main differences between the two treatment groups were abnormal dreams (7% vs. 11%) and anxiety (3% vs. 6%). Unlike abnormal dreams and anxiety disorders, the incidence of depressive disorders (all cause, all severity) was higher in the RPV group (8% vs. 6% in the EFV group). Discontinuation due to depressive disorders was similar between the two groups (4 subjects in each group). Treatment emergent adverse hepatic reactions were similar between the two treatment groups (2% each). Grade 3 and 4 hepatic events occurred <1% in each group. An apparent imbalance in biliary events was observed between the two groups, with greater incidence in the RPV group (7 RPV vs. 2 EFV). The incidence of hepatobiliary events observed in the subset of subjects treated with FTC/TDF as background regimen is similar to what was observed in the overall population.

An early preclinical signal of renal toxicity was observed for RPV when administered at high doses. Overall, the incidence of 'renal and urinary' AEs (regardless of severity, causality) was 8% in the RPV group vs. 6% in the EFV group. The incidence of 'renal' AEs was numerically higher in the RPV group. A case of membranous glomerulonephritis and a case of mesagnioproliferative glomerulonephritis were reported with RPV; a biopsy in the case of membranous glomerulonephritis suggested a drug-related event. The incidence of 'renal failure' was 0.5% in the RPV group and 0.4% in the EFV group. An increase in serum creatinine (SCr) was observed with use of RPV, regardless of background regimen. At Week 24, the mean SCr change from baseline was 0.19 mg/dL (0-0.7) for RPV and 0.13 mg/dL (0 - 5.4) for efavirenz (all subjects). The mean maximum SCr was 1.04 mg/dL (0.53-1.8) for RPV compared to 0.97 (0.6, -6.2) for efavirenz. The effect of RPV on CrCL depended on baseline CrCl, with smaller changes noted in subjects with lower baseline CrCL compared to those with normal baseline CrCl. Subjects with moderate renal function did not worsen over time and few patients transitioned to mild or moderate renal impairment during the trial. Almost all patients returned to baseline after treatment was stopped (2-4 weeks follow-up period).

**8. Financial Disclosures**

None of the investigators that participated in the BA/BE trials, including 103 and 108, have entered into any financial arrangement with the Applicant whereby the compensation to the investigators could be affected by outcome of the study. Further, the investigators were not recipients of payments of other sorts as defined in 21 CFR 54.2(f).

**9. Advisory Committee Meeting**

Not applicable.

**10. Pediatrics**

Not applicable.

**11. Other Relevant Regulatory Issues**

There are no outstanding regulatory issues for this NDA.

## 12. Labeling

The applicant's proposed package insert (label) and carton and container labels have been reviewed by the interdisciplinary review team, as well as by the Division of Risk Management (DRISK), the Division of Drug Marketing, Advertising and Communications (DDMAC) and Division of Medication Error Prevention and Analysis (DMEPA). DMEPA found the applicant's revised container labels and carton labeling received on June 27, 2011 acceptable.

Changes to the proposed label were recommended by the review team. Most changes have been agreed upon by the applicant at the time of completion of this memo. Outstanding changes are minor and primarily editorial in nature.

## 13 Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend that the NDA be approved, pending a recommendation from the Office of Compliance regarding the acceptability of the remaining manufacturing site inspections. The labeling revisions recommended by the review team should be incorporated into the final label.

- Risk Benefit Assessment

The risk-benefit assessment considered several factors:

  - The proposed commercial FDC tablet demonstrated bioequivalence to the approved individual agents under fed conditions, consistent with administration directions for rilpivirine. Thus, the efficacy of the FDC tablet is expected to be similar to that observed in the trials conducted to support approval of rilpivirine.
  - Based on a review of the safety data for subjects receiving TDF/FTC in combination with rilpivirine in C209 and C215, the safety profile of the FDC product is expected to reflect the individual components and new safety signals are expected.

- Recommendation for Postmarketing Risk Management Activities

  No postmarketing risk management activities are required for this application

- Recommendation for other Postmarketing Study Commitments

The following Post-marketing commitment (PMC) was proposed by the CMC and biopharmaceutics reviewers. The Applicant has agreed to conduct the additional dissolution testing. However, the final PMC language has not yet been agreed to by the Applicant at the time of finalization of this CDTL memo.

Collect dissolution profile data from all full-scale batches manufactured during the first year after approval date. The collection of the dissolution data will target the dissolution specifications recommended by the FDA (see bullets below) and will include dissolution testing at Stage 1, 2, or 3 as appropriate.

• For Emtricitabine and Tenofovir Disoproxil Fumarate: Q = (b) (4) at 20 minutes; and
• For Rilpivirine Hydrochloride: Q = (b) (4) at 60 minutes

Submit within 15 months after approval of the NDA, a supplement to NDA 202123 including the final dissolution report with:

• The complete dissolution information/data (i.e., batch #, lot size, individual, mean, max, min, SD, plots, etc.),

• A proposal for the final dissolution specifications based on the overall dissolution data,
• A data analysis with the number/percentage of batches that were tested at Stage 1, 2, or 3 or failed the following dissolution specifications recommended by FDA.

- Recommended Comments to Applicant

  No additional comments to convey to the applicant.

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/s/

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SARAH M ROBERTSON
07/27/2011