OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202123 (S-21, SDN 423)	Original Submission Date: April 23, 2015
Brand Name	Complera
Generic Name	Emtricitabine/rilpivirine/tenofovir disoproxil fumarate
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Gilead
Formulation; strength(s)	Fixed dose combination tablet: emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
Indication	Treatment of HIV-1 infection
Review Type	Pediatric supplement

This review documents and supports the clinical pharmacology reviewer comments for a pediatric supplement that includes revisions to the emtricitabine/rilpivirine/tenofovir disoproxil fumarate U.S. prescribing information, which is approved for the treatment of HIV-1 infection. No new clinical trials were included as part of the supplement.

The applicant, Gilead, submitted a supplement that includes updating the emtricitabine/rilpivirine/tenofovir disoproxil fumarate U.S. prescribing information with dosing recommendations for pediatric subjects 12 years old and older that are already included in the U.S. prescribing information for the emtricitabine and tenofovir disoproxil fumarate fixed dose combination product or single entity rilpivirine. The applicant's changes to the emtricitabine/rilpivirine/tenofovir disoproxil fumarate U.S. prescribing information and the revisions proposed by the Office of Clinical Pharmacology are outlined below in section B.

A) Recommendation

With the exception of the changes proposed by the FDA review team that are outlined in section B, the applicant's revisions to the emtricitabine/rilpivirine/tenofovir disoproxil fumarate U.S. prescribing information are acceptable.

B) Applicant and Clinical Pharmacology reviewer revisions to the emtricitabine/rilpivirine/tenofovir disoproxil fumarate U.S. prescribing information

Clinical pharmacology reviewer note: the review team edits outlined below were accepted by the applicant.

Applicant revisions	Review team revisions
Section 12 Pediatric Patients Emtricitabine has been studied in pediatric subjects from 3 months to 17 years of age. Tenofovir DF has been studied in adolescent subjects from 12 to less than 18 years of age. The pharmacokinetics of rilpivirine have been studied in in pediatric subjects from 12 to less than 18 years of age. For additional information, please consult the Edurant, EMTRIVA, and VIREAD prescribing information.	Section 12 *Clinical pharmacology reviewer note: subsequent to requesting that the applicant include emtricitabine, rilpivirine, and tenofovir (using the disoproxil fumarate formulation) pharmacokinetic data for the 12 to 18 years old age group, the applicant submitted revised labeling language. The review team edits for the revised labeling are highlighted below.* Pediatric trials have not been conducted using the emtricitabine, rilpivirine, tenofovir disoproxil fumarate fixed-dose combination tablets. Pediatric information is based on trials conducted with the individual entites. In pediatric subjects, emtricitabine has been studied from 0 months to 17 years of age and tenofovir DF has been studied in 2 years of age and older. Information on the pharmacokinetics of rilpivirine is currently available only for pediatric subjects from 12 to less than 18 years of age *[See Use in Specific Populations (8.4)]*. *Emtricitabine:* The pharmacokinetics of emtricitabine at steady state were determined in 27 HIV-1-infected pediatric subjects 13 to 17 years of age receiving a daily dose of 6 mg/kg up to a maximum dose of 240 mg oral solution or a 200 mg capsule; 26 of 27 subjects in this age group received the 200 mg emtricitabine capsule. Mean (± SD) C_{max} and AUC were 2.7 ± 0.9 µg/mL and 12.6 ± 5.4 µg•hr/mL, respectively. Exposures achieved in pediatric subjects 12 to less than 18 years of age were similar to those achieved in adults receiving a once daily dose of 200 mg. *Rilpivirine:* The pharmacokinetics of rilpivirine in antiretroviral treatment-naïve HIV-1- infected pediatric subjects 12 to less than 18 years of age

receiving rilpivirine 25 mg once daily were comparable to those in treatment-naïve HIV-1-infected adults receiving ripilvirine 25 mg once daily. There was no clinically significant impact of body weight on rilpivirine pharmacokinetics in pediatric subjects in trial C213 (33 to 93 kg).

Table X-Population Pharmacokinetic Estimates of Rilpivirine 25 mg once daily in Antiretroviral Treatment-Naïve HIV-1-Infected Pediatric Subjects aged 12 to less than 18 years (Data from Phase 2 Trial through Week 48)

Parameter	**Rilpivirine 25 mg once daily N = 34**
AUC_{24h} (ng•h/mL)	
Mean ± Standard Deviation	2424 ± 1024
Median (Range)	2269 (417 - 5166)
C_{0h} (ng/mL)	
Mean ± Standard Deviation	85 ± 40
Median (Range)	79 (7 - 202)

Tenofovir Disoproxil Fumarate: Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected pediatric subjects (12 to less than 18 years). Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 µg/mL and 3.39 ± 1.22 µg•hr/mL, respectively. Tenofovir exposure achieved in these pediatric subjects receiving oral daily doses of VIREAD 300 mg was similar to exposures achieved in adults receiving once-daily doses of VIREAD 300 mg.

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01/13/2016

SHIRLEY K SEO
01/14/2016