CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA	208351
Submission Type	Non-NME NDA [505(b)(1)]
Applicant Name	Gilead
Submission Date	7/1/2015
Generic Name	Emtricitabine (FTC)/Rilpivirine (RPV)/Tenofovir Alafenamide (TAF) (F/R/TAF or FTC/RPV/TAF)
Dosage Form (Strength)	Tablet (200/25/25 mg)
Indication	Treatment of HIV-1 in treatment naïve or virologically suppressed patients aged ≥12 years
Review Team	Mario Sampson, PharmD, Islam Younis, PhD

This is an addendum to the NDA 208351 Clinical Pharmacology review dated 12/1/2015. Included in this review is a summary of clinical pharmacology-related labeling negotiations with the sponsor, which are now complete. A substantial portion of these negotiations occurred after submission of the initial review of this application. As shown below in Table 1, clinical pharmacology-related labeling negotiations were focused on the Drug Interactions (section 7) and Pharmacokinetics (section 12.3) sections, and that FDA and the sponsor reached agreement on all of the issues. Of note are the FDA recommendation to take FTC/RPV/TAF with a meal (versus "take with food" as was the sponsor's initial proposal) and to remove drug interaction information for the effect of efavirenz on TAF (see Table 1). The recommendation to take FTC/RPV/TAF with a meal was made because the food effect between FTC/RPV/TAF is similar to single agent RPV, which is labeled to be taken with a meal, and in our opinion a meal represents a significant quantity of food whereas the term food can connote a highly variable quantity of food. The recommendation to remove drug interaction information for the effect of efavirenz on TAF was made because FTC/RPV/TAF is a complete regimen and should not be taken with efavirenz and because we do not consider efavirenz to be representative of worst case Pgp induction.

Table 1. Summary of clinical pharmacology-related labeling negotiations.

Section	Issue	FDA edits 1/14/16	Sponsor edits 1/27/16	FDA edits 2/4/16	Sponsor edits 2/11/16
Dosing and administration	FTC/RPV/TAF should (b) (4)	Replace with "take with a meal"	Replaced with (b) (4) with comment that data in the NDA supports this.	Replaced with "take with a meal". Included rationale: the food effect between F/R/TAF is similar to single agent RPV, which is labeled to be taken with a meal; in our opinion a meal represents a significant quantity of food (b) (4)	Accepted FDA recommendation
Drug interactions	(b) (4)	Deleted paragraph	(b) (4)		Accepted FDA recommendation
Drug interactions	(b) (4)		Accepted FDA recommendation		
Drug interactions	Clinical significance of increased RPV and TAF exposure	For inhibition of 3A resulting in increased RPV exposure and inhibition of Pgp resulting in increased TAF exposure, added that possible adverse events may result	Accepted FDA recommendation		
Drug interactions	Clinical significance of using FTC/RPV/TAF with QT-prolonging drugs	Change from (b) (4) to "consider alternative medications" in order to be more specific	Accepted FDA recommendation		
Specific Populations	Hepatic impairment		Changed from (b) (4)	Accepted sponsor's recommendation	

			(b) (4) severe hepatic impairment"		
Pharmacokinetics	(b) (4)	Requested that sponsor add (b) (4)	Proposed not to do so to be consistent with the E/C/F/TAF label	Accepted sponsor's recommendation	
Pharmacokinetics	(b) (4)		Added back, stating that it is important to prescribers	Deleted statement with initial rationale	Accepted FDA recommendation
Pharmacokinetics	Renal impairment categories	Asked sponsor to replace the ter (b) (4) with the specific GFR values of the enrolled subjects	Did not address comment	Repeated initial comment	Accepted FDA recommendation
Pharmacokinetics	(b) (4)				Accepted FDA recommendation
Pharmacokinetics	(b) (4)			Accepted sponsor's recommendation	
Pharmacokinetics	(b) (4)				Accepted FDA recommendation

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/s/

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03/30/2016

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03/30/2016