

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202123Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202123

SUPPL #

HFD # 530

Trade Name Complera

Generic Name Emtricitabine/Rilpivirine Hydrochloride/Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablets (FTC/RPV/TDF)

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known August 10, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The sponsor conducted and submitted one bioavailability and two bioequivalence studies to support the approval of this fixed dose combination tablet for the treatment of HIV-1 infection in treatment naïve patients.

The three studies are:

1. Study GS-US-264-0101: Bioequivalence Study of Two, Fixed-dose, Combination Tablet Formulations Containing Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Compared to the Concurrent Administration of the Individual Components

2. GS-US-264-0108: Relative Bioavailability Study of a Fixeddose, Combination Tablet Formulation Containin Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Compared to the Concurrent Administration of the Individual Components

3. Study GS-US-264-0103: Bioequivalence Study of Two, Fixed-dose, Combination Tablet Formulations Containing Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Compared to the Concurrent Administration of the Individual Components

The sponsor is relying on the data from Tibotec's two phase 3 clinical trials (C209 and C215) for Edurant® (rilpivirine) to support the efficacy and safety of the fixed dose combination.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021356	VIREAD (tenofovir disoproxil fumarate) 300 mg Tablets
021752	TRUVADA (emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg) tablets
NDA# 021500	Emtriva (emtricitabine) 200 mg Capsules
NDA# 202022	Edurant (rilpivirine hydrochloride) 25 mg Tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not

independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA 202022

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

NDA 202022

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

IND #

YES

!

! NO

! Explain:

Title: Regulatory Project Manager
Date: August 10, 2011

Name of Office/Division Director signing form: Debra Birnkrant, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA C ONAGA
08/10/2011

DEBRA B BIRNKRANT
08/10/2011

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

Necessary studies would be impossible or highly impracticable because:

- Disease/condition does not exist in children
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

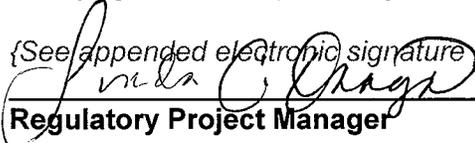
Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Debarment Certification

Gilead Sciences, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act, in connection with this application (NDA 202123, FTC/RPV/TDF fixed-dose combination tablets).



Shalini Gidwani, M.Sc, RAC
Associate Director, Regulatory Affairs

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202123 BLA # N/A	NDA Supplement # N/A BLA STN # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Complera Established/Proper Name: Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Fixed Dose Combination (FTC/RPV/TDF) Dosage Form: Tablets		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): N/A
RPM: Linda C. Onaga, MPH		Division: DAVP
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>8/10/11</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics²</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 4</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other FDA HIV Listserv

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	August 10, 2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval August 10, 2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	August 4, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	October 19, 2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.

❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A <input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Review - July 11, 2011 Resub Filing Checklist - March 8, 2011 RTF Filing Checklist - January 6, 2011
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None See Clinical Review - July 15, 2011 Resub Filing Checklist - March 18, 2011 RTF Filing Checklist - January 20, 2011
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None Review - July 15, 2011 Resub Filing Checklist - February 22, 2011 RTF Filing Checklist - December 22, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None June 30, 2011

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Review - July 8, 2011 Resub Filing Checklist - March 17, 2011 RTF Filing Checklist - January 13, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Product Quality Amendment - August 8, 2011 Product Quality Review - July 15, 2011 Product Quality Resub Filing Checklist - March 17, 2011 Product Quality RTF Filing Checklist - January 6, 2011 Biopharm Review - July 15, 2011 Biopharm Resub Filing Checklist - March 14, 2011 RTF Filing Checklist - December 22, 2010
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	July 15, 2011 (Product Quality Review See Page 167)
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

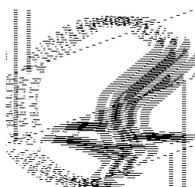
- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

LINDA C ONAGA
08/10/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202123

Drug: FTC/RPV/TDF

Date: July 29, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202123

Please reference your submission dated February 10, 2011. The following comment is being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

For the experiments that was conducted in Addendum 3 for the rilpivirine method validation report:

- 1) Please submit both the regression results (e.g. Watson regression output or spreadsheets with the concentration values and the % bias along with the audit trails) and the chromatograms.
- 2) Please clarify whether the selectivity experiment in Table 8 evaluated a rilpivirine LLOQ sample (1 ng/mL) that was combined with 600 ng/mL of tenofovir and 2400 ng/mL of emtricitabine in the same plasma sample. If not, please clarify how the experiment in Table 8 was conducted.

Please provide the Division with your response no later than Thursday, August 4, 2011.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
07/29/2011

Onaga, Linda

From: Onaga, Linda
Sent: Wednesday, July 27, 2011 11:15 AM
To: 'Shalini Gidwani'
Subject: NDA 202123

Good Morning Shalini,

Please find below an correction that was mistakenly omitted from the labeling comments sent earlier today.

Section 12.3
Under Assessment of Drug Interaction

(b) (4)

This should be updated to the following: Tenofovir had no effect on the C_{max} , AUC and C_{min} of methadone or ethinyl estradiol/norgestimate or the C_{max} and AUC of ribavirin.

Please let me know if you have any additional questions.

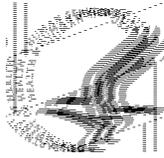
Linda

*Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6321
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/s/

LINDA C ONAGA
07/27/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: July 27, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Yodit Belew, M.D., Clinical Reviewer
Kimberley Struble, Pharm.D., Clinical Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Jules O'Rear, Ph.D., Clinical Virology Team Leader

Subject: NDA 202123 – Labeling Comments #3

The attached Microsoft Word document was sent to the Sponsor on July 27, 2011 and incorporated labeling comments for NDA 202123 (FTC/RPV/TDF) FDC. The submission date of the revised label was on July 25, 2011.

Additionally, there are additional comments for the label:

Please reference your submission dated July 25, 2011. The attached Microsoft Word document was sent to the Sponsor on July 27, 2011 and incorporated labeling comments for NDA 202123 (FTC/RPV/TDF) FDC. The following are labeling comments for your application:

Additional Labeling Comments:

1. The footnote to Table 8 should read for parallel construction (E138K+M184I): "This combination of NNRTI and NNRTI substitutions is a subset of those with the E138K".
2. The change in the following sentence of "10" (July 21 FDA FAX) to (b) (4) (Gilead's response) was not explained: "In the efavirenz arm, none of the (b) efavirenz-resistant

virologic failures were resistant to etravirine at failure.” Please provide a justification for the change.

Please provide your response to the Division no later than by **Monday, August 1, 2011**.

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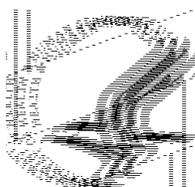
Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

42 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

LINDA C ONAGA
07/27/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202123

Drug: FTC/RPV/TDF

Date: July 21, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Lisa Naeger, Ph.D., Clinical Virology Reviewer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Elsbeth Chikhale, Ph.D., Biopharmaceutics Reviewer
Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader
Yodit Belew, MD, Clinical Reviewer

Subject: Proposed PMC for NDA 202123

Please reference your submission dated February 10, 2011. The following are a Post Marketing Commitment (PMC) and labeling comments for your application:

PMC

We agree to the Phase IV Post-Marketing Commitment (PMC) with the objective of providing the additional dissolution data from full-scale batches that are needed for the setting of the final regulatory dissolution specifications. Please find below the specific PMC language.

1. 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: $Q = \text{■}^{(b)(4)}$ at 20 minutes; and
 - For Rilpivirine Hydrochloride: $Q = \text{■}^{(b)(4)}$ 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.

General Labeling Comments:

1. Please update initial US Approval date to 2001. The US Approval date should reflect the year for the approval of the first product in this fixed dose combination, which is tenofovir disoproxil fumarate.
2. Please update PI with tenofovir DF as the abbreviated version of the established name for tenofovir disoproxil fumarate and remove TDF. The PI should be consistent with one abbreviated form of tenofovir disoproxil fumarate.
3. Please update PPI with the trade name for EDURANT in capital letters.

Clinical Labeling Comments:

4. As discussed during the teleconference, use of TRADENAME in pediatric patients has to be displayed in the Indication and Usage section. The proposed language (with minor revision) ‘TRADENAME is not recommended for patients less than 18 years of age (8.4)’ is acceptable. However, this language should be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION, Indications and Usage, section as well as in Section 1 of the PI, with reference made to Section 8.4. Please refer to current USPIs such as darunavir, etravirine, and raltegravir as examples.

Clinical Pharmacology Labeling Comments:

5. After further discussion, DAVP recommends not including specific information regarding food effects either from the cross trial comparison or from the prescribing information from U.S. approved individual or combination formulations of emtricitabine, tenofovir or rilpivirine.
6. We propose the following revised language for section 12.3 (Effects of Food on Oral Absorption) while results from the food effect trial for the fixed dose combination tablets are pending:

Take TRADENAME with a meal. A food effect trial was not conducted for TRADENAME. Therefore, the specific effect of food with TRADENAME tablets on rilpivirine, emtricitabine and tenofovir exposure has not been established. The

recommendation to administer TRADENAME with a meal is based on the increased exposure that was observed when rilpivirine tablets were administered under fed conditions.

Clinical Virology Comments:

- We recommend in the *Antiviral Activity in Cell Culture* section that the terminology “was not antagonistic” be used throughout (including for emtricitabine and tenofovir) in order to update the language and be consistent within this label. The language in the individual emtricitabine and tenofovir labels can be updated in the near future as they come in for other modifications.

The PID numbers for the Resistance *In Treatment-Naïve Subjects* are listed below.

- In Treatment-Naïve Subjects

In the pooled resistance analysis for subjects receiving rilpivirine in combination with emtricitabine/tenofovir DF in clinical trials C209 and C215 [See *Clinical Studies* (14)], the emergence of resistance was greater in the rilpivirine arms compared to the efavirenz arms (see Table 10). In the combined studies, 44% (34/77) of the virologic failures in the rilpivirine arms had genotypic and phenotypic resistance to rilpivirine compared to 23% (10/43) of the virologic failures in the efavirenz arms who had genotypic and phenotypic resistance to efavirenz. Moreover, phenotypic and/or genotypic resistance to emtricitabine and tenofovir emerged in 51% (39/77) and 9% (7/77) of the rilpivirine virologic failures, respectively, compared to 16% (7/43) and 9% (4/43) of the efavirenz

(b) (4)

TMC278 Virologic Failures (As-Treated) (n=77)

TMC278-C209-0009	TMC278-C209-0548	TMC278-C209-0935
TMC278-C209-0011	TMC278-C209-0555	TMC278-C215-0001
TMC278-C209-0023	TMC278-C209-0573	TMC278-C215-0028
TMC278-C209-0046	TMC278-C209-0574	TMC278-C215-0032
TMC278-C209-0066	TMC278-C209-0594	TMC278-C215-0065
TMC278-C209-0079	TMC278-C209-0612	TMC278-C215-0080
TMC278-C209-0119	TMC278-C209-0629	TMC278-C215-0089
TMC278-C209-0129	TMC278-C209-0636	TMC278-C215-0110
TMC278-C209-0146	TMC278-C209-0667	TMC278-C215-0222
TMC278-C209-0161	TMC278-C209-0679	TMC278-C215-0264
TMC278-C209-0163	TMC278-C209-0683	TMC278-C215-0330
TMC278-C209-0199	TMC278-C209-0703	TMC278-C215-0339
TMC278-C209-0226	TMC278-C209-0724	TMC278-C215-0344
TMC278-C209-0231	TMC278-C209-0745	TMC278-C215-0387
TMC278-C209-0256	TMC278-C209-0750	TMC278-C215-0416
TMC278-C209-0297	TMC278-C209-0760	TMC278-C215-0446
TMC278-C209-0361	TMC278-C209-0768	TMC278-C215-0494
TMC278-C209-0371	TMC278-C209-0779	TMC278-C215-0515
TMC278-C209-0378	TMC278-C209-0784	TMC278-C215-0534

TMC278-C209-0383	TMC278-C209-0787	TMC278-C215-0551
TMC278-C209-0389	TMC278-C209-0807	TMC278-C215-0646
TMC278-C209-0405	TMC278-C209-0835	TMC278-C215-0656
TMC278-C209-0419	TMC278-C209-0857	TMC278-C215-0707
TMC278-C209-0495	TMC278-C209-0871	TMC278-C215-0783
TMC278-C209-0512	TMC278-C209-0887	TMC278-C215-0955
TMC278-C209-0538	TMC278-C209-0915	

EFV Virologic Failures (As-Treated) (n=43)

TMC278-C209-0007	TMC278-C209-0583	TMC278-C215-0266
TMC278-C209-0054	TMC278-C209-0648	TMC278-C215-0281
TMC278-C209-0076	TMC278-C209-0709	TMC278-C215-0287
TMC278-C209-0085	TMC278-C209-0711	TMC278-C215-0419
TMC278-C209-0092	TMC278-C209-0726	TMC278-C215-0472
TMC278-C209-0118	TMC278-C209-0755	TMC278-C215-0540
TMC278-C209-0176	TMC278-C209-0758	TMC278-C215-0591
TMC278-C209-0285	TMC278-C209-0908	TMC278-C215-0621
TMC278-C209-0294	TMC278-C209-0909	TMC278-C215-0625
TMC278-C209-0330	TMC278-C215-0049	TMC278-C215-0806
TMC278-C209-0333	TMC278-C215-0066	TMC278-C215-0835
TMC278-C209-0421	TMC278-C215-0088	TMC278-C215-0860
TMC278-C209-0506	TMC278-C215-0109	TMC278-C215-0879
TMC278-C209-0542	TMC278-C215-0143	
TMC278-C209-0564	TMC278-C215-0228	

TMC278 Subset with >2.5 FC in Rilpivirine susceptibility and Genotypic Evidence of Rilpivirine Resistance (n=34)

TMC278-C209-0009	TMC278-C209-0389	TMC278-C209-0887
TMC278-C209-0011	TMC278-C209-0495	TMC278-C215-0001
TMC278-C209-0066	TMC278-C209-0512	TMC278-C215-0032
TMC278-C209-0079	TMC278-C209-0573	TMC278-C215-0110
TMC278-C209-0119	TMC278-C209-0594	TMC278-C215-0330
TMC278-C209-0129	TMC278-C209-0636	TMC278-C215-0339
TMC278-C209-0146	TMC278-C209-0745	TMC278-C215-0344
TMC278-C209-0161	TMC278-C209-0768	TMC278-C215-0416
TMC278-C209-0163	TMC278-C209-0779	TMC278-C215-0515
TMC278-C209-0231	TMC278-C209-0787	TMC278-C215-0534
TMC278-C209-0297	TMC278-C209-0807	
TMC278-C209-0361	TMC278-C209-0871	

EFV Subset with EFV Resistance (n=10)

C209-0118	FTC TDF
C209-0007	FTC TDF
C209-0092	FTC TDF
C209-0176	FTC TDF
C209-0285	FTC TDF
C209-0333	FTC TDF
C209-0648	FTC TDF
C209-0711	FTC TDF
C215-0109 (V106M)	FTC TDF
C215-0860 (V106M)	FTC TDF

TMC278 ARM: FTC Genotypic or Phenotypic Resistance (n=39)

TMC278-C209-0009	TMC278-C209-0745
TMC278-C209-0011	TMC278-C209-0768
TMC278-C209-0023	TMC278-C209-0779
TMC278-C209-0066	TMC278-C209-0787
TMC278-C209-0079	TMC278-C209-0807
TMC278-C209-0119	TMC278-C209-0835
TMC278-C209-0129	TMC278-C209-0871
TMC278-C209-0146	TMC278-C209-0887
TMC278-C209-0161	TMC278-C215-0001
TMC278-C209-0163	TMC278-C215-0032
TMC278-C209-0226	TMC278-C215-0065
TMC278-C209-0231	TMC278-C215-0080
TMC278-C209-0297	TMC278-C215-0110
TMC278-C209-0361	TMC278-C215-0330
TMC278-C209-0389	TMC278-C215-0339
TMC278-C209-0495	TMC278-C215-0344
TMC278-C209-0512	TMC278-C215-0416
TMC278-C209-0573	TMC278-C215-0515
TMC278-C209-0594	TMC278-C215-0534
TMC278-C209-0636	

TMC278 ARM: TDF Genotypic or Phenotypic Resistance (n=7)

TMC278-C209-0023
TMC278-C209-0361
TMC278-C209-0389
TMC278-C209-0512
TMC278-C209-0745
TMC278-C209-0779
TMC278-C215-0001

EFV Arm: FTC Genotypic or Phenotypic Resistance (n=7)

TMC278-C209-0007	EMT FC 3.3
TMC278-C209-0085	M184M/V
TMC278-C209-0176	M184V
TMC278-C209-0333	M184I/V/M
TMC278-C209-0711	M184V
TMC278-C215-0109	EMT FC 5.3
TMC278-C215-0860	M184M/V

EFV Arm: TDF Genotypic or Phenotypic Resistance (n=4)

TMC278-C209-0007	TDF FC 1.8
TMC278-C215-0109	K65R TDF FC 2.5
TMC278-C215-0540	TDF FC 1.8
TMC278-C215-0835	K65R/K

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
07/21/2011

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 20, 2011
TIME: 2:30 PM – 3:30 PM
APPLICATION: NDA 202123
SPONSOR: Gilead Sciences, Inc
DRUG NAME: emtricitabine/rilpivirine/tenofovir disoproxil fumarate
200/25/300mg fixed dose combination tablet

TYPE OF MEETING: Teleconference

MEETING CHAIR: Yodit Belew, MD

MEETING RECORDER: Linda C. Onaga, MPH

FDA ATTENDEES:

- Yodit Belew, M.D., Clinical Reviewer, Division of Antiviral Products
- Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, OTS/OCP/DCPIV
- Vikram Arya, Ph.D., Acting Clinical Pharmacology Team Leader, OTS/OCP/DCPIV
- Lisa Naeger, Ph.D., Clinical Virology Reviewer, Division of Antiviral Products
- Jules O’Rear, Ph.D., Clinical Virology Team Leader, Division of Antiviral Products
- Karen Winestock, CPMS, Division of Antiviral Products
- Linda Onaga, M.P.H., Regulatory Project Manger, Division of Antiviral Products

GILEAD SCIENCES ATTENDEES:

- David Pizzuti, M.D., Vice President, Regulatory Affairs
- Paul Tomkins, Senior Director, Regulatory Affairs
- Shalini Gidwani, M.Sc, Associate Director, Regulatory Affairs
- Martine Kraus, Ph.D., Senior Director, Regulatory Affairs-Labeling, Advertising & Promotion
- Brian Kearney, Pharm.D., Senior Director, Clinical Pharmacology
- Srinu Ramanathan, Ph.D., Associate Director, Clinical Pharmacology
- Alena Jandourek, M.D., Director, Clinical Research
- Michael Miller, Ph.D., Senior Director, Clinical Virology

DISCUSSION POINTS:

Gilead requested a brief teleconference with the Division of Antiviral Products to discuss the Division’s revisions to the FTC/RPV/TDF fixed dose combination (FDC) label currently under NDA review. Gilead acknowledged the Division’s proposals to update Section 7 (Drug Interactions) and Section 12.3 (Clinical Pharmacokinetics). Gilead accepted the Division’s

proposal to delete [REDACTED] (b) (4) as FTC/RPV/TDF FDC is a complete regimen, indicated for use in treatment naïve patient.

Points of Discussion:

Section 7- Drug Interactions and Section 12.3 Clinical Pharmacokinetics

1. Gilead accepted the Division's proposal to include all the pharmacokinetic interaction data in Section 12.3, regardless of whether the interactions were clinically relevant. Gilead proposed that if no clinically relevant interactions were observed, it be presented in a running text for the NRTIs. Currently, this information is presented in a tabular format in the revised PI.

[REDACTED] (b) (4)

However, the Division is open to including running text language for the NRTIs in section 12.3. The Division provided an example of preferred running text language. For example, the effect of emtricitabine on tenofovir could be stated as: There was no change in tenofovir C_{max} and AUC but the C_{min} was increased by 20% when emtricitabine was coadministered with tenofovir.

Gilead requested clarification as to whether the Division was moving towards including all pharmacokinetic interaction data (i.e. regardless of outcome of DDI). Gilead stated that in previous labels such as Atripla, if the result of the DDI was deemed not clinically relevant (horizontal arrow), no additional clinical information was added into the PI.

The Division stated that the current policy is to include interpretation text in Section 7.9 and to present the DDI results (regardless of the result of the interaction- increase, decrease, no effect) in a tabular format under Section 12.3.

The division agreed to allow Gilead to propose changes to the pharmacokinetic interaction tables for the NRTIs if the content of the information in the tables could be readily converted to running text. Gilead stated that they would evaluate further whether converting the tables to running text would be feasible.

2. Gilead expressed their concerns about the addition of the food effect data. Gilead acknowledged the importance of providing appropriate guidance regarding the impact of food, as RPV exposures are significantly impacted by food. [REDACTED] (b) (4)

[REDACTED]

(b) (4)

It was brought to Gilead's attention that the Division provided to Gilead as part of the fixed dose combination tablet development program the option of conducting a food effect study with the fixed dose combination tablet and Gilead chose not to conduct one at that time.

Gilead stated their commitment to conduct a food effect trial after the approval of the NDA (b) (4)

The Division restated their disagreement with their proposal. The Division suggested adding a statement "COMPLERA must be administered with food" immediately after "Effects of Food on Oral Absorption" section to overcome the potential misreading of the cross trial comparison. In addition, under Indications and Usage section, it is recommended to be taken with meal.

Gilead stated they remain concerned that including the information from (b) (4)

The Division will further discuss this topic internally and provide a response to Gilead.

Section 12.4 Microbiology- Antiviral Activity

3. Gilead commented on the reorganization of the data in this section. Gilead presented all information in alphabetical order and wanted to know why the Division's revisions place it out of order.

The Division rationale to placing it out of order was to show that rilpivirine was the important anchor drug in this fixed dose combination. However, the division agreed to have the data in the original format, so that it aligns with the rest of the section

4. Gilead requested clarification as to why the Division deleted (b) (4) and replaced it with "was not antagonistic" in the antiviral activity subsection.

The Division responded that the revision was consistent with other labeling. The Division recommended in the 'Antiviral Activity in Cell Culture' section that the terminology "was not antagonistic" be used throughout (including for emtricitabine and tenofovir) in order to update the language and be consistent within this label. The language in the individual emtricitabine and tenofovir labels can be updated in the near future as they come in for other labeling modifications. (b) (4)

(b) (4) The Division does not want to give a claim that is not clinically relevant.

Gilead understood the Division's rationale and will continue to discuss this internally.

5. Gilead inquired about how the Division calculated the percentages and numbers in the treatment naïve HIV-1 infected subjects section.

The Division will provide Gilead the PID numbers for the resistance in the Treatment Naïve Subjects.

Section 1.0 Indications and Usage

6. Gilead acknowledged the Division's proposal of including text in the Indication regarding "product not recommended for use in < 18". Gilead stated that this information is already provided in the *Use in Specific Populations – Pediatrics Section* of the label and aligns with the information that was stated in the rilpivirine label.

The Division stated that this information should be included in the Indication and Use section of the label. We recognized that this was not included in the rilpivirine label, and will be included once a supplement is submitted.

Gilead asked if this was going to be a universal change.

The Division responded that the majority of the recently approved labels without pediatric approvals have this information in the Indications and Usage section.

Section 17 Patient Information

7. Gilead stated most common side effects listed in the PPI is slightly different from the highlights section of the label. Gilead proposed deleting the following side effects: vomiting, stomach pain or discomfort, skin discoloration, (b) (4) and pain to align with the highlights.

The Division stated that the adverse events listed in the PPI do not have to be limited only to adverse events listed in the HIGHLIGHTS section. The Division referred to the Atripla and Truvada PPIs as examples. The Division stated that adverse events included in the post-marketing section are not included in the PPI unless such events were subsequently elevated and included in the Warnings and Precautions section. Therefore, Gilead can delete (b) (4) from the adverse events section of the PPI, but 'vomiting', 'stomach pain' or 'discomfort', 'skin discoloration', and 'pain' should remain.

Gilead proposed (b) (4)

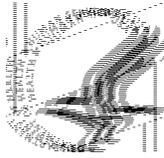
The Division accepted this alternative approach.

End of Minutes

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/s/

LINDA C ONAGA
08/03/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: July 18, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Yodit Belew, M.D., Clinical Reviewer
Kimberley Struble, Pharm.D., Clinical Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Lisa Naeger, Ph.D., Clinical Virology Reviewer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Rao Kambhampati, Ph.D., ONDQA CMC Reviewer
Stephen Miller, Ph.D., ONDQA CMC Team Leader

Subject: NDA 202123 – Labeling Comments #2

The attached Microsoft Word document was sent to the Sponsor on July 18, 2011 and incorporated labeling comments for NDA 202123 (FTC/RPV/TDF) FDC. The submission date of the revised label was on June 24, 2011.

Please provide your response to the Division no later than by **Friday, July 22, 2011**.

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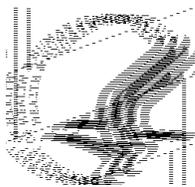
Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

47 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

LINDA C ONAGA
07/18/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202123

Drug: FTC/RPV/TDF

Date: June 28, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202123 Additional information request

Please reference your submission dated February 10, 2011. The following comment is being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) For the rilpivirine method that was validated at [REDACTED] (b) (4) please clarify whether the QCs, blanks and calibrations standards were prepared in lithium or sodium heparin anticoagulated plasma.
- 2) For the GS-264-103 and GS-264-108 trials, for rilpivirine, please clarify whether blood samples were drawn in tubes with lithium heparin or sodium heparin as an anticoagulant.
- 3) For the GS-264-103 and GS-264-108 trials, for rilpivirine, please clarify whether the QCs, blanks and calibrations standards were prepared in lithium heparin or sodium heparin anticoagulated plasma.
- 4) For the GS-264-103 and GS-264-108 trials, for emtricitabine and tenofovir, please confirm that blood samples were drawn in tubes with K2EDTA as an anticoagulant.
- 5) For the emtricitabine and tenofovir method that was validated at [REDACTED] (b) (4) please confirm that the QCs, blanks and calibrations standards were prepared in K2EDTA anticoagulated plasma.

- 6) For the GS-264-103 and GS-264-108 trials, for emtricitabine and tenofovir, please clarify whether the QCs, blanks and calibrations standards were prepared in K2EDTA anticoagulated plasma.
- 7) For addendum one for the (b)(4) method validation report (PBRL-RD-1197), please clarify why an experiment was conducted comparing sodium and lithium heparin anticoagulated QCs.
- 8) For the additional 60 day long term stability experiment with all 3 analytes combined together that is being conducted at (b)(4), please confirm that long term stability at both -20C and -70C is being evaluated.

Please provide the Division with your response no later than Friday, July 8,2011.

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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
06/28/2011



NDA 202-123

INFORMATION REQUEST

Gilead Science, Inc.
Attention: Sujatha Narayan
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Narayan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/rilpivirine/tenofovir disoproxil fumarate Tablets 200 mg/25 mg/300 mg..

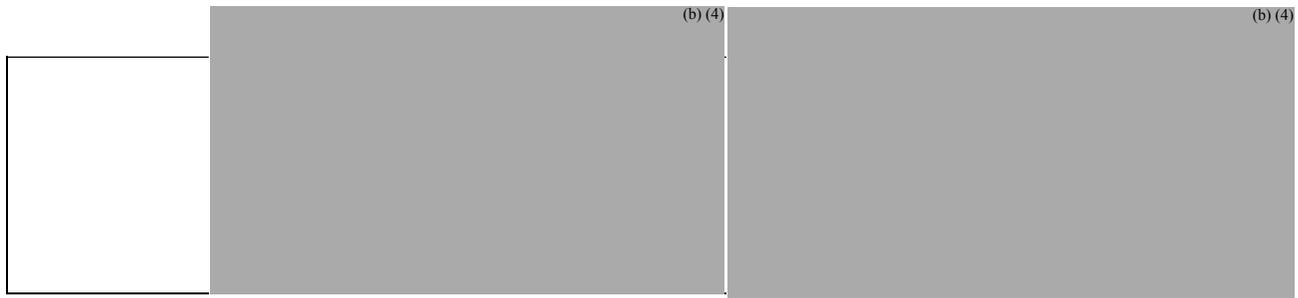
We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. In order to continue our evaluation of your NDA, we request your response by July 7, 2011.

We acknowledge your June 20, 2011 responses to our earlier information requests. Your responses are currently under review.

1) Given current manufacturing standards and the quality of the FTC/RPV/TDF tablets as demonstrated in the batch release and stability data, we recommend the following changes to the acceptance criteria for the (b)(4) and shelf-life degradation product content in the specification for drug product:

Test	Gilead Proposed Acceptance Criterion	FDA Recommended Acceptance Criterion
Degradation Product Content	<p data-bbox="527 1409 690 1438">(b)(4)</p> <p data-bbox="430 1451 901 1669">At Release: <i>For emtricitabine</i> NMT a total of (b)(4) FTC-related degradation products, and NMT (b)(4) each of any unspecified FTC-related degradation product.</p> <p data-bbox="430 1711 868 1890"><i>For rilpivirine</i> NMT a total of (b)(4) RPV-related degradation products, with NMT (b)(4) each of any unspecified RPV-related degradation product.</p>	<p data-bbox="933 1409 1209 1438">Not more than (b)(4)</p> <p data-bbox="933 1451 1079 1522">At Release: No change</p>

	<p><i>For tenofovir DF</i> NMT a total of (b) (4) TDF-related and unidentified degradation products, with NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) TDF-r and NMT (b) (4) each of any other unidentified degradation product.</p>	
	<p><i>During Shelf-Life:</i> <i>For emtricitabine</i> NMT a total of (b) (4) FTC-related degradation products, with NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) each of any unspecified FTC-related degradation product</p> <p><i>For rilpivirine</i> NMT a total of (b) (4) RPV-related degradation products, with NMT (b) (4) each of any unspecified RPV-related degradation product</p> <p><i>For tenofovir DF</i> NMT a total of (b) (4) TDF-related and unidentified degradation products, with NMT (b) (4) NMT (b) (4) NMT (b) (4), NMT (b) (4), NMT (b) (4) (b) (4) NMT (b) (4) NMT (b) (4) (b) (4) NMT (b) (4) NMT (b) (4) (b) (4) NMT (b) (4) each of any unspecified TDF-related degradation product, and</p>	<p><i>During Shelf-Life:</i> <i>For emtricitabine</i> NMT a total of (b) (4) FTC-related degradation products, with NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) each of any unspecified FTC-related degradation product</p> <p><i>For rilpivirine</i> No change</p> <p><i>For tenofovir DF</i> NMT a total of (b) (4) TDF-related and unidentified degradation products, with NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) (b) (4) NMT (b) (4) NMT (b) (4) NMT (b) (4) (b) (4), NMT (b) (4) (b) (4) NMT (b) (4) each of any unspecified TDF-related degradation product, and NMT (b) (4) each of any other</p>



2) It is our understanding that for attributes where no release acceptance criterion is listed, the shelf-life acceptance criterion applies at batch release, and the observed value would be reported on the Certificate of Analysis. To clarify this point, we recommend that the specification for the FTC/RPV/TDF Tablets list all attributes (with the appropriate acceptance criteria) under both “Release” and “Shelf-Life.” Please provide a revised Specification Table in Section 3.2.P.5.1.

If you have any questions, contact Jeannie David, Regulatory Project Manager, at (301) 796-4247, or jeannie.david@fda.hhs.gov.

Sincerely,

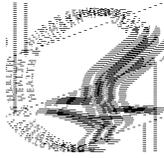
{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
06/24/2011
For Rapti Madurawe



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: June 17, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Yodit Belew, M.D., Clinical Reviewer
Kimberley Struble, Pharm.D., Clinical Team Leader
Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader

Subject: NDA 202123 – Comments for May 31, 2011 Submission

A Microsoft Word version of the following label with the review team's suggested revisions and comments was sent to the sponsor via email on June 17, 2011.

In addition, please find below additional comments from the Division of Medication Error Prevention and Analysis on the container label (30 count) and carton labeling (1x30 count) as well as the clinical review team.

Division of Medication Error and Analysis Comments:

1. We note the placeholder, "Tradename" is being used as a substitute for the proprietary name. Once the proprietary name is approved, ensure that the established name is at least ½ the size of the proprietary name and ensure the established name has a prominence commensurate with the prominence with which the proprietary name appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
2. Revise the presentation of the established name so that the strength of each ingredient appears below the established name and not within. Revise to read as follows:

TRADENAME

(Emtricitabine, Rilpivirine, Tenofovir Disoproxil Fumarate) Tablets
200 mg/25 mg/300 mg

3. Relocate the net quantity, 30 tablets, to the upper right corner of the principal display panel so that it is away from the product strength.
4. Relocate the statement, “Gilead Access Program” to the side panel. The principal display panel should be reserved for pertinent information. Additionally, this statement crowds the principal display panel.

Clinical Review Team Comments Pertinent to Section 6 (Adverse Reactions):

We recognize your approach to adverse reactions labeling is to (b) (4), (b) (4), reported in $\geq 2\%$ of subjects treated with rilpivirine or efavirenz, plus tenofovir DF + emtricitabine.

Although we agree with selecting of subset of the subjects who received TDF/FTC as background regimen, (b) (4)

(b) (4)
Although the information can be displayed using more than one approach, we believe the following approach is best:

- Prior to the availability of Atripla, individual USPI were available for efavirenz, tenofovir and emtricitabine. Prescribers were familiar with the adverse reactions associated with the individual drugs. Unlike Atripla, the marketing of Complera is close to the approval of rilpivirine, where knowledge to rilpivirine among prescribers is limited. Therefore, the adverse reactions labeling for Complera should look very similar to rilpivirine.
- One approach to reach this goal is to limit the Adverse Reaction Table to ADRs associated to rilpivirine or efavirenz. The table would be followed by paragraphs describing the adverse events reported for tenofovir and emtricitabine from other clinical trials.
- Having ADR table similar to what is included in the rilpivirine table will lead to less confusion about adverse reactions associated with the newly approved component of Complera, rilpivirine.
Please note, because there was a difference in the calculated incidence of “depression” between the Agency and Tibotec Inc., when reporting ADR for “depression” in Table 1, you may need to obtain the USUBJID for those subjects in order to discern which subjects received TDF/FTC as background regimen.
- The Agency’s guidance on labeling discourages from including all adverse events, regardless of causality as adverse reactions (see Guidance for Industry - Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format). **“The definition of adverse reactions does not include all adverse events observed during use of a drug.** It is limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug (§ 201.57(c)(7)). Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are

based on factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs.”

Based on the rationale above, we recommend you revise your adverse reaction table. As stated above, paragraphs describing adverse reactions previously described for TDF/FDC should be sufficient in providing a complete adverse reactions profile for the FDC drug, Complera.

Please provide this information to the Division no later than by **Friday, June 24, 2011**

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
06/17/2011



NDA 202-123

INFORMATION REQUEST

Gilead Science, Inc.
Attention: Sujatha Narayan
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Narayan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/rilpiverine/tenofovir disoproxil fumarate Tablets 200 mg/25 mg/300 mg.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response by June 22, 2011.

Drug Substance:

1. Provide the batch analysis results of the drug substance batches that were used for the manufacturing of the pivotal clinical, stability, scale up, and commercial batches of the drug product. Include the following batches: 1136091022; 1136062003; 05-1090648; 05-1090757; 05-1090758; 05-1090648; 05-1090758; and 05-1090759.
2. Analyze the emtricitabine (FTC) drug substance batches including stability batches for the presence of [REDACTED] (b) (4) contents using the newly developed HPLC and UPLC methods that can detect these impurities.
3. Provide a complete description of the method that is used for the determination of the impurities in emtricitabine drug substance. Include the chromatograms of the emtricitabine sample solution and standard solution in the description.

Drug Product:

4. Provide spectroscopic evidence (1H NMR, 13C NMR, MS, IR, etc.) in support of the proposed structure for the two degradants [REDACTED] (b) (4)
5. Provide the [REDACTED] (b) (4) Total FTC impurities content of the drug product batch BY1011B.

6. Provide stability study results of the drug product batches BY1011B; BY1013B, and BY1014B that were manufactured by using rilpivirine (RPV) drug substance of (b) (4) and tenofovir disoproxil fumarate (TDF) drug substance of (b) (4).
7. Provide available stability data for the commercial size batches of the drug product, if available.
8. In the Document No. TM-138.00 (Identity, Strength, and Degradation Product Content of FTC/RPV/TDF Tablets), Figure 8 (Chromatogram of sample solution by HPLC at (b) (4)) and Figure 18 (Chromatogram of sample solution by UPLC at (b) (4)) contain several peaks that were not identified. Please provide the identities and quantities of the impurities/degradation products in those peaks.
9. In the justification for Microbial Limits test, you have stated that the preparatory testing for these tablets (FTC/RPV/TDF) show that the three active ingredients cause inhibition, requiring dilutions of 1:50 or more in order to promote microbial growth. In addition, FTC/RPV/TDF tablets are a solid oral dosage form (b) (4). Please provide data that support the inherent antimicrobial activity of the drug product and also provide the (b) (4) results of the drug product stability lots.
10. Please revise the proposed dissolution acceptance criteria as follows:
 - For emtricitabine and tenofovir disoproxil fumarate: $Q = (b) (4)$ at 20 minutes
 - For rilpivirine: $Q = (b) (4)$ at 45 minutes

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247, or email at jeannie.david@fda.hhs.gov.

Sincerely,

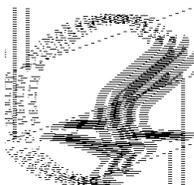
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Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
06/02/2011
on behalf of Rapti D. Madurawe



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202123

Drug: FTC/RPV/TDF

Date: May 25,2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202123 Additional information request

Please reference your submission dated February 10, 2011. The following comment is being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) Please clarify the following issues for the (b) (4) 60-0961 report:
 - a) Please confirm that the selectivity, freeze thaw, and long term stability experiments were conducted with all 3 analytes combined together in the same sample (5 ng/mL of emtricitabine and tenofovir for the selectivity experiment and 15 ng/mL or 2400 ng/mL of emtricitabine and tenofovir in combination with 300 ng/mL of rilpivirine for the freeze thaw and long term stability experiments). The titles of the tables in the report only indicate that either tenofovir or emtricitabine were evaluated in the presence of rilpivirine.
 - b) Please confirm that the selectivity, freeze thaw, and long term stability experiments with all 3 analytes combined together were conducted in K2EDTA anticoagulated plasma.
- 2) For the additional freeze thaw and long term stability experiments for the rilpivirine assay that are being conducted at (b) (4), please confirm that rilpivirine concentrations

of 3 ng/mL and 1600 ng/mL are being evaluated in combination with emtricitabine and tenofovir concentrations of 2400 ng/mL and 600 ng/mL, respectively.

Please provide the Division with your response no later than Friday, June 10, 2011.

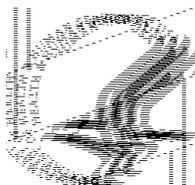
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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/25/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202123

Drug: FTC/RPV/TDF

Date: May 23, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202123 Additional information request

Please reference your submission dated February 10, 2011. The following comment is being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

1. The trial reports for the GS-US-264-103 and GS-US-264-108 trials indicate that actual sampling times, when feasible, were used in the noncompartmental analysis. For the pc.xpt and the adpc.xpt files, please add an additional column to both files with the actual postdose sampling times for both the GS-US-264-103 and GS-US-264-108 trials.

Please provide the Division with your response no later than Friday, June 3, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/23/2011

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 23, 2011
TIME: 2:45 PM
APPLICATION: NDA 202123
SPONSOR: Gilead Sciences, Inc
DRUG NAME: emtricitabine/rilpivirine/tenofovir disoproxil fumarate 200/25/300 mg fixed dose combination tablet

TYPE OF MEETING: Teleconference

MEETING CHAIR: Kim Struble, Pharm.D.

MEETING RECORDER: Linda C. Onaga, MPH

FDA ATTENDEES:

- Yodit Belew, M.D., Clinical Reviewer, Division of Antiviral Products
- Kim Struble, Pharm.D., Clinical Team Lead, Division of Antiviral Products
- Linda Onaga, M.P.H., Regulatory Project Manger, Division of Antiviral Products

GILEAD SCIENCES ATTENDEES:

- David Pizzuti, M.D., Vice President, Regulatory Affairs
- Pamela Danagher, M.Sc, Senior Director, Regulatory Affairs
- Shalini Gidwani, M.Sc, Associate Director, Regulatory Affairs
- Martine Kraus, Ph.D., Senior Director, Regulatory Affairs-Labeling, Advertising & Promotion
- Andrew Cheng, M.D., Senior Vice President, Development Operations

DISCUSSION POINTS:

Division requested a brief teleconference with Gilead to discuss the label for the FTC/RPV/TDF fixed dose combination (FDC) product currently under NDA review. We requested that Gilead submit a brand new label for the fixed dose combination. Currently, there are major inconsistencies between the information present in the FDC label and Tibotec's recently approved Edurant[®] (rilpivirine) label.

Although a final decision has not been made, the Division is considering including the full trial results from C209 and C215 in the ADR and Clinical Studies section of the label and includes text stating the results in subjects receiving TDF/FTC were similar to the overall trial results.

Gilead expected that upon approval of Edurant[®], that a harmonization between the two labels would be necessary. The company is currently working on revising the label to address the differences.

The Division requested that Gilead provide an updated label by May 31, 2011. Gilead agreed to the request.

Gilead inquired about that status of the inspections for the various sites. As Monday, the site inspections have been scheduled and everything is on track for the PDUFA Goal Date of August 10, 2011.

End of Minutes

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/s/

LINDA C ONAGA
05/25/2011

From: Onaga, Linda
To: "Shalini Gidwani";
Pamela Danagher;
Subject: NDA 202123 Pediatric Plan
Date: Monday, May 16, 2011 12:15:07 PM

Good Morning Shalini and Pam,

As discussed this morning, we ask that you provide a brief draft pediatric development plan for the FTC/RPV/TDF FDC under review. This plan will assist the Pediatric Research Committee (PeRC) in reviewing your deferral request. The draft plan should include general discussion points on the type of trial(s), (e. g. PK, antiviral activity, and safety of FDC).

We request that this information be provided by close of business on Thursday, May 19, 2011.

Thank you,

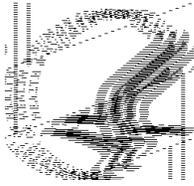
Linda

*Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6321
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.0759
Fax: 301.796.9883
Email: linda.onaga@fda.hhs.gov*

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/s/

LINDA C ONAGA
05/17/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202123

Drug: FTC/RPV/TDF

Date: May 13, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202123 Additional information request

Please reference your submission dated February 10, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) The trial reports for the 103 and 108 trials states that the tenofovir and emtricitabine reference products are the "commercial drug product". Please confirm that these are the US commercially marketed tenofovir and emtricitabine drug products.

Please provide the Division with your response no later than Friday, May 20, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/13/2011



NDA 202123

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, California 94404

ATTENTION: Shalini Gidwani, M.Sc., RAC
Associate Director, Regulatory Affairs

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) resubmission dated February 10, 2011, received February 10, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Emtricitabine, Rilpivirine, and Tenofovir Disoproxil Fumarate Tablets, 200 mg/25 mg/300 mg.

We also refer to your February 14, 2011, correspondence, received February 15, 2011, requesting review of your proposed proprietary name, Complera. We have completed our review of the proposed proprietary name, Complera and have concluded that it is acceptable.

The proposed proprietary name, Complera, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your February 14, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Linda Onaga at (301) 796-0759.

Sincerely,

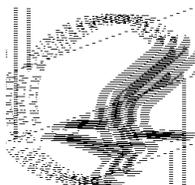
{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/13/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: May 10, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202-123 Additional information request

Please reference your submission dated February 10, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) In order to better understand the food effect of the fixed dose combination tablet, please conduct and submit a comparison of the food effect (fed/fasted) for the rilpivirine, emtricitabine and tenofovir analytes for formulation 3 based on the pharmacokinetic data from the 103 and 108 trials.

Please provide the Division with your response no later than Wednesday, May 18, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
05/10/2011



NDA 202-123

FILING COMMUNICATION

Gilead Sciences, Inc
Attention: Shalini Gidwani, M.Sc. RAC
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani

Please refer to your New Drug Application (NDA) dated February 10, 2011 received February 10, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for emtricitabine/rilpivirine/tenofovir disoproxil fumarate 200/25/300 mg fixed dose combination tablet.

We also refer to your submissions dated September 3, 2010, October 19, 2010, November 5, 2010, November 23, 2010, November 30, 2010, December 3, 2010, December 10, 2010, December 20, 2010, December 22, 2010, February 10, 2011, and February 16, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We also request that you submit the following information:

Clinical:

1. Please submit Individual Subject Data Listings (Data Tabulation Dataset in .xpt format) for study GS-US-264-0101.
2. Please revise the "Pediatric Study Deferral Request" to include anticipated dates for protocol(s) submission(s), study(ies) completion, and final study report(s) submission.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

3. Please avoid error prone abbreviations, symbols, and dose designations. Please update the labeling with the following:

- a. Do not use [REDACTED] (b) (4) since it may be mistaken for the number 1. Please update the labeling with “per” instead of [REDACTED] (b) (4). Use 5 mg per 10 mL.
 - b. For the text, do not use the symbol for less than [REDACTED] (b) (4). Please spell the word in the labeling. The symbols can be used in tables.
4. Highlights Section:
- a. Use in Specific Population (Page 1),
 - i. Please remove [REDACTED] (b) (4) from the Highlights section of the physician insert.
 - ii. Please remove the following [REDACTED] (b) (4)
5. Table of Content
- a. The Highlights and Table of Contents do not fit on one page, please insert the Table of Contents on page 2 of the labeling.
 - b. Section 17 should be listed as, **17 PATIENT COUNSELING INFORMATION**
6. Full Prescribing Information
- a. Section 17 should be listed as 17 PATIENT COUNSELING INFORMATION.
{See FDA-Approved Patient Labeling (Patient Information)}
7. Patient Information
- a. Remove [REDACTED] (b) (4)

We request that you resubmit labeling that addresses these issues by May 2, 2011. The resubmitted labeling will be used for further labeling discussions. Please ensure the SPL formatted labeling is consistent with the word version.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Antiviral Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full deferral request is denied.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

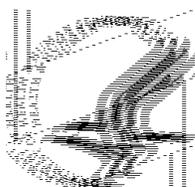
{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DEBRA B BIRNKRANT
04/22/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: April 19, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202-123 SN 15 Additional information request

Please reference your submission dated March 9, 2011. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

- 1) Please clarify whether additional long-term stability data for rilpivirine in the presence of emtricitabine and tenofovir beyond the documented 39 days at -20°C and -70°C will be generated. A minimum of 60 days of long terms stability data for rilpivirine in the presence of emtricitabine and tenofovir -20°C and -70°C is recommended based on the PK sampling and sample analysis information from the GS-US-264-103 and the GS-US-264-108 trials.
- 2) The response to FDA's comments that were submitted on March 9, 2011 indicated that the choice of QC concentrations for emtricitabine and tenofovir were based on published C_{max} values. However, the QC concentrations of 500 ng/mL for emtricitabine and 200 ng/mL for tenofovir are not representative of the C_{max} values that were observed in the GS-US-264-103 and the GS-US-264-108 trials. Emtricitabine mean C_{max} concentrations of ~2000 ng/mL were observed in the two trials and for tenofovir, mean C_{max} concentrations of 300-400 ng/mL were observed in the two trials.

- a. DAVP recommends that you conduct the rilpivirine selectivity experiment and repeat the freeze thaw and long-term stability experiments for rilpivirine in the presence of emtricitabine and tenofovir using a QC concentration for emtricitabine of 2400 ng/mL and a QC concentration of 600 ng/mL for tenofovir.
 - b. If the selectivity, freeze thaw and long term stability experiments are repeated, please provide information on timelines for availability of the experimental data.
- 3) Please clarify whether a selectivity experiment for rilpivirine in the presence of emtricitabine and tenofovir will be conducted as previously recommended.

Please provide the Division with your response no later than Monday, May 2, 2011.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
04/19/2011



NDA 202-123

PRIORITY REVIEW DESIGNATION

Gilead Sciences, Inc
Attention: Shalini Gidwani, M.Sc. RAC
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) dated February 10, 2011 received February 10, 2011 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for emtricitabine/rilpivirine/tenofovir disoproxil fumarate fixed dose combination tablet, 200 mg FTC/25 mg RPV/300 mg TDF.

We also refer to your submission dated September 3, 2010, October 19, 2010, November 5, 2010, November 23, 2010, November 30, 2010, December 3, 2010, December 10, 2010, December 20, 2010, December 22, 2010, February 10, 2011, and February 16, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is August 10, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 20, 2011.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before April 25, 2011.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager, at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DEBRA B BIRNKRANT
04/05/2011



NDA 202-123

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MS
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/rilpivirine/tenofovir disoproxil fumarate fixed dose combination tablet, 200 mg FTC/25 mg RPV/300 mg TDF.

We also refer to the teleconference between representatives of your firm and the FDA on February 7, 2011. The purpose of the meeting was to discuss the Refuse to File letter issued to NDA 202-123.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Division Director
Division of Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A

Meeting Date and Time: February 7, 2011 3:30 – 4:40pm EST

Application Number: 202-123

Product Name: Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Fixed Dose Combination Tablet, 200 mg FTC/25 mg RPV/300 mg TDF

Indication: Treatment of HIV-1 infection

Sponsor/Applicant Name: Gilead Sciences, Inc

Meeting Chair: Debra Birnkrant, MD

Meeting Recorder: Linda C. Onaga

FDA ATTENDEES

1. Dave Roeder, Associate Director for Regulatory Affairs, Office of Antimicrobial Products
2. Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
3. Jeff Murray, M.D., MPH, Deputy Director, DAVP
4. Kim Struble, Pharm.D., Medical Team Leader, DAVP
5. Yodit Belew, M.D., Medical Officer, DAVP
6. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, OTS, Office of Clinical Pharmacology (OCP),
7. Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Leader, DAVP
8. Mark Powley, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
9. Mark Seaton, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
10. Stephen Miller, Ph.D., Acting Branch Chief, Office of New Drug Quality Assessment (ONDQA)
11. Rao Kambhampati, Ph.D., Chemistry Reviewer, ONDQA
12. Brantley Dorch, Regulatory Project Manager, OSE
13. Jeannie David, M.S., Regulatory Project Manager, ONDQA
14. Linda C. Onaga, M.P.H., Regulatory Project Manager, DAVP
15. Karen Winestock, Chief, Project Management Staff, DAVP

SPONSOR ATTENDEES

1. Norbert Bishhofberger, Ph.D., Executive Vice President, Research and Development
2. Taiyin Yang, Ph.D., Senior Vice President, Pharmaceutical Development and Manufacturing
3. Andrew Cheng, MD, Ph.D., Senior Vice President, Development Operations and HIV Therapeutic Area Head
4. Tom Weber, Ph.D., Vice President, Analytical Development

5. David Pizzuti, MD, Vice President, Regulatory Affairs
6. Pamela Danagher, M.Sc, Senior Director, Regulatory Affairs
7. Sujatha Narayan, M.Sc, Director, RA CMC, Regulatory Affairs
8. Shalini Gidwani, M.Sc, Associate Director, Regulatory Affairs
9. Grushenka Wolfgang, Ph.D., Vice President, Drug Safety Evaluation
10. Anne Chester, Ph.D., Senior Director, Drug Safety Evaluation

1.0 BACKGROUND

Gilead Sciences, Inc. (Gilead) is developing emtricitabine (FTC), rilpivirine (RPV) and tenofovir disoproxil fumarate (TDF) fixed-dose combination (FDC) tablet for the treatment of HIV-1 infection. On November 23, 2010, Gilead submitted the final piece of the new drug application (NDA) to market the new FDC tablet in the United States. Within the first 60 days of the review cycle, the Division of Antiviral Products (DAVP) held a multi-disciplinary meeting to discuss the application. At this meeting, it was determined that information on the recently identified (b) (4) degradants would be needed before an action could be taken. Because the data missing was essential to the approvability of the product and had not been submitted, the DAVP determined the application was incomplete. Gilead received a Refusal to File (RTF) letter from the Division on January 20, 2011, which outlined the deficiencies and information needed to complete the NDA submission.

On January 27, 2011, Gilead requested a Type A meeting with the DAVP to discuss the next steps that will enable a fileable NDA. The Division provided feedback and additional comments to the proposed questions on February 4, 2011.

The objectives provided by Gilead for the February 7, 2011 meeting were as follows:

1. Confirm specific content requirements for a fileable NDA
2. Understand the status of the interdisciplinary activities that were ongoing at the Agency, during the fileability determination period of NDA 202123, in order to take the appropriate steps towards a fileable NDA

2. DISCUSSION

Gilead provided the Division with an update on the progress to re-submit the NDA.

- The Electronic Submission Group at the FDA advised Gilead that they could retain their current NDA number and resubmit the deficiencies outlined in the RTF letter in a subsequent submission. Furthermore, Gilead should very clearly state in the cover letter that it would be a resubmission of the NDA.
- Gilead will also resubmit the proprietary trade name request again, as instructed in the preliminary comments.
- Gilead understood that the review clock for NDA 202-123 will start over and the entire application will be reviewed again to determine if it is fileable.

Gilead requested additional discussions on their response to FDA's Additional comments 1-3. The FDA's additional comments from the February 4, 2011 preliminary meeting responses are in italics, and meeting discussion is in regular font.

Additional FDA Comment 1:

- 1. Please provide the Division with an updated timeline of planned submissions to address the deficiencies in the Refuse-to-File letter.*

Meeting Discussion: Updated Timeline of Planned submissions to address the deficiencies in the RTF letter (Slides 2 and 3)

- Gilead stated their intent to address all the deficiencies outlined in the RTF letter and resubmit the NDA to the Agency no later than February 14, 2011.
- The Division requested a guidance map that directs the reviewers to the updated sections in the application.
- Gilead clarified that Module 3 had been updated with the (b) (4) information .

Additional FDA Comment 2 and 3:

- 2. Given the profound acceleration of degradation rates observed for FTC/RPV/TDF tablets which were exposed to 25degC/65%RH conditions outside the container, please provide available data on (b) (4) levels in emtricitabine drug substance, and the other drug products containing emtricitabine, when studied in similar "open-dish" conditions. Please submit this information to NDA 202-123, and to the other NDAs for all Gilead emtricitabine products.*
- 3. Please provide an updated timeline for your submission of information on the (b) (4) degradants to 202-123 and to the approved NDAs, if possible prior to the February 7, 2011 teleconference.*

Meeting Discussion: Slides 4 and 5

- The Division requested that Gilead cross reference NDA 21-752 (Truvada), which provides an update to the pharmacology/toxicology study reports including information that outlines why the re-analysis is appropriate.
- The Division will provide Gilead with instructions on how to hyperlink from one NDA to another, which will be useful for this NDA and future supplements.
- Gilead confirmed that future submissions related to the (b) (4) degradants will be submitted to the Truvada and Atripla NDAs as prior approval supplements in April 2011. Gilead does not intend to conduct open-dish studies on emtricitabine drug substance because current information indicates that the (b) (4) degradants (b) (4) (b) (4)
- Gilead confirmed that the open dish results for the FDC tablet would be included in the February 14, 2011 submission. The data will be similar to that which was provided in

the December 13, 2010 meeting package for NDAs 21-500, (b) (4), 21-752, and 2 (b) (4) but with a slightly different presentation.

- The Division asked if there was any new pharmacology/toxicology data other than what was submitted to NDA 21-752. Gilead confirmed that the same information that was submitted to NDA 21-752 will be the same for NDA 202-123 resubmission.
- The Division finds Gilead's submission plans outlined in their slide presentation acceptable.

2.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

- Gilead will also resubmit the proprietary trade name request again, as instructed in the preliminary comments.
- The Division requested a guidance map in Module 1 that directs the reviewers to the updated sections in the application.
- The Division will provide Gilead with additional information on how to hyperlink from one NDA to another, which will be useful for this NDA and future supplements.

5.0 ATTACHMENTS AND HANDOUTS

- Attached is the slide presentation for the January 7, 2011 meeting, developed by Gilead Sciences.

5 pages has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

DEBRA B BIRNKRANT
03/09/2011



NDA 202-123

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

Gilead Sciences, Inc
Attention: Shalini Gidwani, M.Sc. RAC
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our January 20, 2011 refusal to file letter for the following:

Name of Drug Product: emtricitabine/rilpivirine/tenofovir disoproxil fumarate fixed dose combination tablet, 200 mg FTC/25 mg RPV/300 mg TDF

Date of Application: February 10, 2011

Date of Receipt: February 10, 2011

Our Reference Number: NDA 202-123

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 11, 2011 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Linda C. Onaga, MPH Regulatory Project Manager, at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
02/17/2011



NDA 202-123

MEETING PRELIMINARY COMMENTS

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MS
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/rilpivirine/tenofovir disoproxil fumarate Tablet, 200 mg FTC/25 mg RPV/300 mg TDF.

We also refer to your January 27, 2011 correspondence, received January 28, 2011 requesting a meeting to discuss the Refusal to File Letter issued to NDA 202-123.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 7, 2011 at 3:30 pm to 4:30 pm EST between Gilead Sciences, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Questions:

- 1) Gilead wishes to discuss with the Agency its options to provide a fileable NDA, and to discuss the anticipated review process once the application is filed.
 - Gilead notes that FTC/RPV/TDF for the treatment of HIV-1 infection has been granted Fast Track designation, and NDA 202123 had progressed as a rolling submission. Given this fact, we wish to explore whether there is an option to submit the outstanding information outlined in the RTF letter as a further and final addition to a rolling application.
 - Should this not be a viable option, we wish to discuss other options to quickly provide the outstanding information to assure a fileable NDA, and to reinstate the review process.

FDA Response:

Please contact CDER's electronic submissions coordinator at esub@fda.hhs.gov for guidance on retaining your current NDA number.

- 2) Gilead wishes to seek clarity on specific topics regarding the review process that was underway as part of NDA 202123. Specifically:
 - Under NDA 202123, Gilead was in the process of providing responses to review questions. Currently, a response to Agency comments dated 7 January 2011 was pending with a due date of 28 January 2011. Gilead proposes to include responses to these questions in Module 1.11 of the planned filing. Does the Agency concur?

FDA Response:

Yes, we agree that it is appropriate to provide the questions and responses in Module 1.11 ("Information Not Covered Under Modules 2 to 5"). However, where the responses are important for understanding technical sections of the NDA (e.g., Characterization of Impurities, Justification of Specifications, Analytical Procedures) at a minimum those sections should contain a hyperlink to Module 1.11, and in many cases those sections should also be updated to show the new information. This is important so that the current technical sections of the eCTD will accurately reflect the new information about the (b) (4) degradation pathway.

An alternative approach which has some advantages for reviewers is to provide the full response to each question in whichever technical section is most appropriate. In that approach, the questions and short responses with a hyperlink to the technical section can be provided in Module 1.11.

- Under NDA 202123, Gilead had provided responses to Clinical Pharmacology and ONDQA questions (Attachment 4). Gilead wishes to confirm if these amendments will need to be resubmitted?

FDA Response:

You do not need to resubmit the information provided in the Jan 31, 2011 amendment to 21-752 (14-day gavage study, in silico predictions, and justification for revised analyses), but the appropriate technical sections in Module 3 and 4 of 202-123 should be revised to include hyperlinks to the 21-752 amendment.

- As part of the NDA submission, Gilead had submitted its proposed tradename for review to DMEPA. The request for tradename review was submitted on 09 November 2010. Gilead would like to understand if this review is currently on hold and will the process need to be reinitiated?

FDA Response:

You will have to resubmit a new request for review of proprietary name when you submit your complete response.

- Can we retain the current NDA number?

FDA Response:

Please see our response to question 1.

Additional FDA comments:

Regulatory

1. *Please provide the Division with an updated timeline of planned submissions to address the deficiencies in the Refuse to File letter.*

Chemistry, Manufacturing, and Controls

2. *Given the profound acceleration of degradation rates observed for FTC/RPV/TDF tablets which were exposed to 25degC/65%RH conditions outside the container, please provide available data on (b)(4) levels in emtricitabine drug substance, and the other drug products containing emtricitabine, when studied in similar "open-dish" conditions. Please submit this information to NDA 202-123, and to the other NDAs for all Gilead emtricitabine products.*
3. *Please provide an updated timeline for your submission of information on the (b)(4) degradants to 202-123 and to the approved NDAs, if possible prior to the February 7, 2011 teleconference.*

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
02/04/2011



NDA 202-123

MEETING REQUEST GRANTED

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MS
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/rilpivirine/tenofovir disoproxil fumarate Tablet.

We also refer to your January 27, 2011 correspondence requesting a meeting to discuss the Refuse to File Letter issued to NDA 202-123. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The teleconference is scheduled as follows:

Date: February 7, 2011
Time: 3:30 pm – 4:30 pm EST
Phone Arrangements: Provided by Gilead Sciences, Inc.
Call-in Number: 1-888-811-6083
Meeting ID # 2088

Tentative CDER Participants:

1. Dave Roeder, Associate Director for Regulatory Affairs, Office of Antimicrobial Products
2. Debra Birnkrant, M.D., Director, Division of Antiviral Products (DAVP)
3. Jeff Murray, M.D., MPH, Deputy Director, DAVP
4. Kim Struble, Pharm.D., Medical Team Leader, DAVP
5. Yodit Belew, M.D., Medical Officer, DAVP
6. Sarah Robertson, Pharm D., Clinical Pharmacology Team Leader, OTS, Office of Clinical Pharmacology (OCP),
7. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, (OCP)
8. Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Leader, DAVP
9. Mark Powley, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
10. Mark Seaton, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
11. Pritam Verma, Ph.D., Pharmacology/Toxicology Stephen Miller, Ph.D., Acting Branch Chief, Office of New Drug Quality Assessment (ONDQA)

12. Rao Kambhampati, Ph.D., Chemistry Reviewer, ONDQA
13. Dorota Matecka, Ph.D., Acting Chemistry Team Lead, ONDQA
14. Thomas Oliver, Ph.D., Branch Chief, Branch VI, ONDQA
15. LaToya Toombs, Safety Evaluator Staff, Division of Medication Error Prevention and Analysis (DEMPA)
16. Irene Chan, Safety Evaluator Staff Team Leader, Division of Medication Error Prevention and Analysis (DEMPA)
17. Brantley Dorch, Regulatory Project Manager, OSE
18. Jeannie David, M.S., Regulatory Project Manager, ONDQA
19. Linda C. Onaga, M.P.H., Regulatory Project Manager, DAVP
20. Karen Winestock, Chief, Project Management Staff, DAVP

If you have any questions, call me at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
02/01/2011



NDA 202-123

REFUSAL TO FILE

Gilead Sciences, Inc.
Attention: Shalini Gidwani, MS
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani

Please refer to your November 23, 2010 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for emtricitabine/rilpivirine/tenofovir disoproxil fumarate Tablet 200 mg FTC/25 mg RPV/300 mg TDF.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

The application does not contain sufficient information to establish the safe levels of two recently identified emtricitabine degradants (b) (4) and to assure that these impurities are controlled at or below the safe level during storage and use of the drug product. Specifically, the information requested in the Dec 20, 2010 FDA letter (#1-7, listed below), plus the additional points shown in italics, should be submitted in order to complete the application.

1. Submit justification and data to support your proposal that (b) (4)
2. Submit data to show how the (b) (4) impurities change over time.
3. Re-evaluate the stability batches and the retained commercial batches for impurities (b) (4) with the new analytical method and submit these data.
4. Submit evidence to support that there are no genotoxicity structure alerts for (b) (4)
5. Submit the 2003 toxicological evaluation of stressed Truvada tablets provided in NDA 21-752 ("A 14-day oral gavage toxicity study comparing non-degraded and degraded TDF/FTC in Sprague-Dawley Rats", Ref. No. 000, Module 4, volume 01, page 217).

6. Submit your position paper for a revised Certificate of Analysis. *In addition to the scientific justification for the revised Certificates of Analysis for the 2003 toxicology samples, also reconcile the analytical results for the FTC/RPV/TDF tablets presented in Table 4.6-1 (Nov 11, 2010; 21-752 Seq. No. 0367) with the open-dish study reports presented in the Sept 3, 2010 submission to NDA 202,123 (Attachment 3.2.P.8.3-6). The latter report does not show the expected mass balance deficit.*
7. Submit documentation of how the samples from the above-referenced toxicological evaluation were stored from the time of the study to the present. *Given the much more rapid degradation seen in tablets exposed to moisture, submit information on how the 2003 samples were protected from moisture while stored at -20°C, and provide an estimate of the proportion of the [REDACTED]^{(b)(4)} that may have formed over 7 years under those conditions.*

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Linda C Onaga, Regulatory Project Manager, at (301) 796-0759.

Sincerely yours,

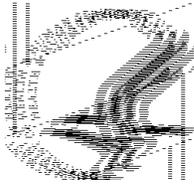
{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DEBRA B BIRNKRANT
01/20/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: January 7, 2011

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202-123 SN 9 Additional information request

Please reference your submission dated December 22, 2010. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

Comments for (b) (4) study number 60-0961:

- 1) Please provide further information regarding why a rilpivirine concentration of 300 ng/mL instead of the rilpivirine low (3 ng/mL) and high (1600 ng/mL) QC values was evaluated in the selectivity, interference, freeze thaw stability and long term stability experiments for the emtricitabine and tenofovir analytical method with rilpivirine analyte added to K2EDTA anticoagulated plasma.
- 2) Please provide further information regarding the rationale for specific emtricitabine and tenofovir concentration values and the emtricitabine and tenofovir concentration values that are being evaluated in the selectivity, interference, freeze thaw stability and long-term stability experiments for the rilpivirine analytical method with emtricitabine and tenofovir analytes added to heparin anticoagulated plasma.

- 3) Please clarify whether the cause of the failure of the calibration standards and QCs in runs 2 and 3, respectively, to meet acceptance criteria were further investigated. In addition, please clarify whether both analytes (emtricitabine and tenofovir) failed to meet acceptance criteria.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
01/07/2011



NDA 202-123

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc
Attention: Shalini Gidwani, M.Sc. RAC
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Gidwani

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: emtricitabine/rilpivirine/tenofovir disoproxil fumarate
Tablet, 200 mg FTC/25 mg RPV/300 mg TDF

Date of Application: November 23, 2010

Date of Receipt: November 23, 2010

Our Reference Number: NDA 202-123

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 23, 2011 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager, at (301) 796-0759.

Sincerely,

{See appended electronic signature page}

Linda C. Onaga, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
12/02/2010

From: Sharma, Khushboo
Sent: Friday, November 26, 2010 10:20 AM
To: 'shalini.gidwani@gilead.com'
Cc: David, Jeannie C; Onaga, Linda
Subject: Information Request for NDA 202-123

Dear Ms. Gidwani,

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 202-123. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

1) Please provide the type of testing (e.g., stability, batch release etc.) performed for each testing site in the CMC section of the application.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov and Jeannie.David@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

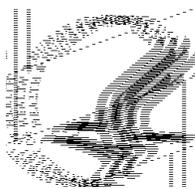
Thank you

*Khushboo Sharma, MBA
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270*

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/s/

KHUSHBOO SHARMA
11/26/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: November 15, 2010

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Yodit Belew, MD, Clinical Reviewer
Kim Struble, Pharm.D., Clinical Team Leader

Subject: NDA 202-123 SN 1 Additional information request

Please reference your submission dated October 19, 2010. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

A) GS-US-264-108 bioanalysis (rilpivirine)

- 1) In run #2, please provide further information on whether the reasons for the failure of the QCs were further investigated.
- 2) Please clarify whether the temperature(s) that long term sample stability was evaluated at (-20°C) by Tibotec was the storage temperature(s) throughout the life cycle of the rilpivirine PK samples from the following two trials: GS-US-264-108 and GS-US-264-103 (e.g. at the clinical trial site and the bioanalytical laboratory).

B) GS-US-264-103 bioanalysis (emtricitabine and tenofovir)

- 1) In run #5, please provide further information on whether the reasons for the failure of the QCs were further investigated.

2) Please clarify the temperature(s) that the emtricitabine and tenofovir PK samples were stored at from the following two trials: GS-US-264-108 and GS-US-264-103 (e.g. at the clinical trial site and the bioanalytical laboratory).

3) Please clarify whether the emtricitabine plasma concentrations that were greater than the upper limit of quantification were reanalyzed using a 5 fold or a 10 fold dilution factor.

C) Other comments

1) Please clarify the storage temperature that freeze/thaw stability and long term stability is being evaluated at with all three analytes combined together in plasma matrix.

Please provide this information to the Division no later than **December 10, 2010**.

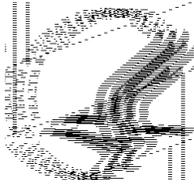
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Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
11/15/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 202-123

Drug: FTC/RPV/TDF

Date: October 6, 2010

To: Shalini Gidwani, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences

From: Linda C. Onaga, MPH, Regulatory Project Manager

Concur: Stanley Au, Pharm.D., Clinical Pharmacology Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader

Subject: NDA 202-123 – Additional information request

Please reference your submission dated September 3, 2010. The following comments are being conveyed on behalf of Dr. Au, the primary clinical pharmacology reviewer for your application.

A) Method validation for emtricitabine and tenofovir

- 1) In the following runs, please clarify whether the following reference standards were recertified prior to using in the analytical runs below:
 - a. runs #12 through 13: tenofovir internal standard
 - b. run #14: tenofovir and the tenofovir internal standard
- 2) Please provide further information on whether the cause(s) of the carryover that exceeded the acceptance criteria in runs 5 and 6 were further investigated and clarify why the increased carryover did not impact the analytical data that was generated from these runs.
- 3) Please clarify whether post preparative stability was determined over 138 hours (section 12.9.3) or 314 hours (Tables 24 and 25).

B) Method validation for rilpivirine

- 4) Please provide further information on whether the cause(s) of the carryover that exceeded the acceptance criteria in all analytical runs with Blank 1 (validation and calibration samples) were further investigated and clarify why the increased carryover did not impact the analytical data that was generated for the method validation.
- 5) If the information is available, please provide information on whether carryover was an issue for the GS-US-264-108 trial.
- 6) Please clarify whether extraction recovery for rilpivirine was evaluated as part of the partial validation. If the experiment was not conducted, please provide a rationale.
- 7) During the partial rilpivirine method validation at [REDACTED] (b) (4) and bioanalysis of rilpivirine plasma samples from the GS-US-264-103 and GS-US-264-108 trials, was the potential conversion of rilpivirine to the [REDACTED] (b) (4) monitored for? If yes, please describe the extent to which conversion to the [REDACTED] (b) (4) was observed.

C) GS-US-264-103 bioanalysis (emtricitabine and tenofovir)

- 8) Please clarify whether the emtricitabine plasma concentrations that were greater than the upper limit of quantification were reanalyzed using a 10 fold dilution factor.
- 9) For runs 13 and 26, please clarify why the runs were accepted for emtricitabine and tenofovir only, respectively. If the runs did not meet the acceptance criteria for the respective analytes, were the causes further investigated?

D) GS-US-264-103 bioanalysis (rilpivirine)

- 10) In run #9, please provide further information on whether were the reasons for the failure of the QCs were further investigated.
- 11) Please clarify why a 200 ng/mL QC was added and whether additional precision and accuracy experiments were conducted that included this QC concentration.

E) General questions

- 12) Please clarify whether the following validation experiments were conducted with all three analytes (emtricitabine, tenofovir, and rilpivirine) combined together in plasma matrix:
 - a. specificity/selectivity and potential cross interference
 - b. long term sample stability
 - c. freeze thaw stability

Please provide this information to the Division no later than by **Friday, November 5, 2010**.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-0759 if you have any questions regarding the contents of this transmission.

Linda C. Onaga, M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LINDA C ONAGA
10/06/2010