

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022577Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22577 and 21356 S-038

SUPPL #

HFD # 530

Trade Name VIREAD

Generic Name tenofovir disoproxil fumarate

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known January 18, 2012

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) and 505(b)(1) SE9 manufacturing change with clinical data

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.

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?

3

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?

Yes

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# 21356

VIREAD (tenofovir disoproxil fumarate) Tablets

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#

NDA#

NDA#

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:

Study GS-US-104-0352: A Phase III, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

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"):

Study GS-US-104-0352: A Phase III, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy

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 # 52,849 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Katherine Schumann, M.S.
Title: Regulatory Project Manager, DAVP
Date: December 14, 2011

Name of Office/Division Director signing form: Jeffrey Murray, M.D., M.P.H.
Title: Deputy Director

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

/s/

KATHERINE SCHUMANN
01/18/2012

JEFFREY S MURRAY
01/18/2012

1.3.3. 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 Food, Drug and Cosmetic Act in connection with this application.

[See appended electronic signature]

Pamela Danagher, Senior Director
Regulatory Affairs

1.3.3 Debarment Certification

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date <small>(yyyy-MM-dd hh:mm)</small>
Pamela Danagher	Regulatory Affairs eSigned	2011-05-19 17:24

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22577 21356	NDA Supplement # S-000 S-038	If NDA, Efficacy Supplement Type: Original SE-9 (manufacturing change with clinical data)
Proprietary Name: Viread Established/Proper Name: tenofovir disoproxil fumarate Dosage Form: oral powder tablets		Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): N/A
RPM: Katherine Schumann, M.S.		Division: Division of Antiviral Products (DAVP)
<p><u>NDA's:</u> 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><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> 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><u>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.</u></p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 18, 2012</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): 3</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <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 checked="" type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input checked="" 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 type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

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 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>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Yes
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) NDA 22577: Approval, 1/18/2012 NDA 21356 S-038: Approval, 1/18/2012
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. 	January 13, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 16, 2011
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

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

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	January 13, 2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	June 16, 2011
<ul style="list-style-type: none"> • 	N/A
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	NDA 22577: January 13, 2012 NDA 21356 S-038: December 23, 2011
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Not applicable
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 1/18/2012 <input checked="" type="checkbox"/> DMEPA 12/09/2011 <input checked="" type="checkbox"/> DRISK 12/14/2011 <input checked="" type="checkbox"/> DDMAC 12/16/2011 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	8/11/2011
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>10/26/2011</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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>) 	<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 December 9, 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 December 21, 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 December 23, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input type="checkbox"/> None December 19, 2011
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input type="checkbox"/> None December 1, 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		
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> 		<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 		<input type="checkbox"/> None January 18, 2012
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 		<input type="checkbox"/> None NDA 22577: CMC: December 23, 2011 Biopharm: December 27, 2011 NDA 21356 S-038: CMC Review #2: January 12, 2012 CMC Review #1: December 22, 2011 Biopharm: December 21, 2011
❖ 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 (OMPQ/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 type="checkbox"/> None Refer to pharm/tox section above for a review of the inactive ingredient ethylcellulose
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		22577 November 8, 2011 21356 S-038 November 8, 2011
<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) (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) (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 checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input 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/

KATHERINE SCHUMANN
01/18/2012

From: Schumann, Katherine
Sent: Tuesday, January 17, 2012 1:52 PM
To: 'Rebecca Mock'
Cc: 'Dara Wambach'; Regulatory Archives; David, Jeannie C; Miller, Stephen
Subject: NDA 22577 Viread Oral Powder - PMCs

Importance: High

Dear Rebecca,

We have reviewed your submission dated January 16, 2011, received January 17, 2012, containing a Quality Information amendment with two proposed Post-Marketing Commitments (PMCs), as agreed upon during the teleconference held between the Agency and Gilead Sciences on January 13, 2012.

The Agency has made several minor revisions to your proposed wording of the PMCs. I am including the complete wording below with the changes identified in blue text.

PMC-1

During the filling of one **commercial full-scale** Viread oral powder lot, execute a stratified sampling plan to determine the potency of the powder blend and verify that potency variation does not occur due to segregation. Include individual measurements of strength from at least one single scoop sample per container for containers spanning the full packaging run. Include both individual values and statistical analysis of the data in the study report.

The timetable you submitted on January XX, 2012, states that you will conduct this study according to the following schedule:

Study/Trial Completion: 12/18/2012
Final Report Submission: 01/18/2013

PMC-2

Submit data from a simulated in-use study of strength per scoop where a bottle is exhaustively sampled one scoop at a time. **Use a bottle subjected to appropriate simulated shipping conditions so that it is representative of a bottle obtained by a patient.** Include data from each scoop sampled and appropriate statistical analysis in the study report.

The timetable you submitted on January XX, 2012, states that you will conduct this study according to the following schedule:

Study/Trial Completion: 12/18/2012
Final Report Submission: 01/18/2013

Please review the changes and **submit a statement of your agreement** (regarding the two PMCs and the corresponding, proposed timelines) **to the NDA as soon as possible**, no later

than 1/18/2012 (tomorrow).

You can address the submission to Jeannie, who will be back in the office shortly. Please also copy me.

Please let me or Jeannie know if you have any questions.

Warm Regards,

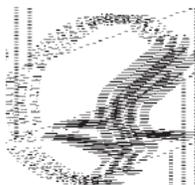
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6237
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
01/17/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 22577
21356 S-038

Drug: Viread (tenofovir disoproxil fumarate) oral powder

Date: January 13, 2012

To: Dara Wambach, M.A., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Katherine Schumann, M.S., Regulatory Project Manager, DAVP

Subject: NDA 22577 Viread Oral Powder and NDA 21356 S-038 Viread Tablets –
Comments Regarding Proposed Labeling

Please refer to your New Drug Application (NDA) and supplemental New Drug Application (sNDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD (tenofovir disoproxil fumarate) oral powder and tablets. Also refer to your submission dated January 11, 2011, received January 12, 2011, containing the revised package insert (PI) and patient package insert (PPI) for VIREAD. The following comments regarding the PI and PPI are being communicated on behalf of the review team. Please refer to the attached PI and PPI for specific comments.

Please submit a response to this correspondence by Tuesday, January 17, 2012.

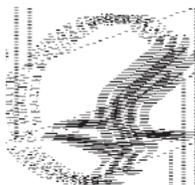
Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
01/13/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 22577
21356 S-038

Drug: Viread (tenofovir disoproxil fumarate) oral powder

Date: January 10, 2012

To: Dara Wambach, M.A., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Katherine Schumann, M.S., Regulatory Project Manager, DAVP

Subject: NDA 22577 Viread Oral Powder and NDA 21356 S-038 Viread Tablets –
Comments Regarding Proposed Labeling

Please refer to your New Drug Application (NDA) and supplemental New Drug Application (sNDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD (tenofovir disoproxil fumarate) oral powder and tablets. Also refer to your submission dated December 23, 2011, received December 27, 2011, containing the revised package insert (PI) and patient package insert (PPI) for VIREAD. The following comments regarding the PI and PPI are being communicated on behalf of the review team. Please refer to the attached PI and PPI for specific comments.

Please submit a response to this correspondence by Tuesday, January 17, 2012.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
01/10/2012



NDA 22-577

INFORMATION REQUEST

Gilead Sciences, Incorporated
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viread® (tenofovir disoproxil fumarate) Oral Powder, 40 mg/gram.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We understand that you are working with the DMF holder to address several of these points, so we request your complete written response submitted to NDA 22-577 by January 6, 2011.

Please refer to the bulk drug product information provided in NDA 22-577. It appears that (b) (4) granules (b) (4) contain a disproportionately high weight percent of the drug substance (i.e. superpotent). We are concerned that the drug substance (b) (4)

(b) (4) Please explain this observation and in addition respond to the following:

- a. (b) (4)
- b. (b) (4)
- c. Provide assay data by (b) (4) for differently sized granules (b) (4)
- d. Provide particle size distribution and assay by (b) (4) data for the final bulk drug product blend.

If any of the above information is currently not available to establish [REDACTED] (b) (4) of the drug occurs during the manufacturing process, please indicate when you would be able to provide this data.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Katherine Schumann, Regulatory Project Manager the Office of New Drugs (Katherine.Schumann@fda.hhs.gov).

If you have any questions regarding this CMC letter, call Jeannie David at (301) 796-4247.

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/

RAPTI D MADURAWA
01/04/2012

Schumann, Katherine

From: Schumann, Katherine
Sent: Thursday, December 22, 2011 2:14 PM
To: 'Dara Wambach'
Cc: Regulatory Archives
Subject: NDA 22577 Viread Oral Powder - Additional Labeling Comments

Hi Dara,

As I mentioned over the phone, the review team has one additional labeling comment for the VIREAD PI currently under review. The following proposed labeling revision pertains to section 12.3 Pharmacokinetics.

In a single-dose bioequivalence study conducted under non-fasted conditions (dose administered with 4 oz. applesauce) in healthy adult volunteers, the mean C_{max} of tenofovir was ^(b)₍₄₎ 26% lower for the oral powder relative to the tablet formulation. Mean AUC of tenofovir was similar between the oral powder and tablet formulations.

This change is being suggested because the clinical pharmacology team has done a reanalysis of Study 0312 (health adult BE study) removing two subjects (20 and 21). The removal of these subjects was recommended by DSI based upon inspection findings.

Warm Regards,

Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6237
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
12/29/2011

From: Schumann, Katherine
Sent: Wednesday, December 21, 2011 2:09 PM
To: 'Dara Wambach'
Cc: 'Regulatory Archives'; 'Thomas Haberberger'
Subject: RE: NDA 22577 and NDA 21356 S-38 Additional Labeling Comments

Dear Dara,

I have one additional comment regarding the labeling that was communicated to me after I sent the correspondence below. I hope you can take this into consideration when you are addressing the other comments:

Please do not use the Microcaps[®] trade name when describing Viread[®] oral powder in the labeling documents of NDA 22577.

When you have time, please send me a quick note to confirm you have received this additional labeling comment.

Warm Regards,

Katie
(301) 796-1182

From: Schumann, Katherine
Sent: Wednesday, December 21, 2011 1:18 PM
To: Dara Wambach
Cc: Regulatory Archives; Thomas Haberberger
Subject: NDA 22577 and NDA 21356 S-38 Additional Labeling Comments

Hi Dara,

In response to your submission of the revised VIREAD labeling on December 12, the Division is sending a second set of labeling comments. Please find the correspondence and track-changed PI and PPI attached. I am also attaching an MS Word version of the labeling for your convenience.

Please let me know if you have any questions.

Warm Regards,

Katie

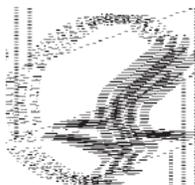
<< File: 2011_12_21 NDA 22577 Labeling Comments with PI.pdf >> << File: 2011_12_20 FDA comments NDA 22577 PI.doc >>

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
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10903 New Hampshire Ave., Bldg. 22, Room 6237
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Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
12/21/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 22577
21356 S-038

Drug: Viread (tenofovir disoproxil fumarate) oral powder

Date: December 21, 2011

To: Dara Wambach, M.A., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Katherine Schumann, M.S., Regulatory Project Manager, DAVP

Subject: NDA 22577 Viread Oral Powder and NDA 21356 S-038 Viread Tablets –
Comments Regarding Proposed Labeling

Please refer to your New Drug Application (NDA) and supplemental New Drug Application (sNDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD (tenofovir disoproxil fumarate) oral powder and tablets. Also refer to your submission dated December 12, 2011, containing the revised package insert (PI) and patient package insert (PPI) for VIREAD. The following comments regarding the PI, PPI, container labels and carton labels are being communicated on behalf of the review team.

ALL LABELS AND LABELING

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).
2. Increase the size and prominence of the middle portion of the NDC numbers (e.g. xxxxx-XXXX-x). Pharmacists use this portion of the NDC number to ensure the correct product is dispensed.
3. Revise the dosage statement [REDACTED] ^{(b) (4)} to read “Usual Dosage: See Prescribing Information”

PACKAGE INSERT & PATIENT PACKAGE INSERT

- Please refer to the attached PI and PPI for specific comments.

CARTON & CONTAINER LABELS

Oral Powder

- Revise the strength statement from (b) (4) to read “40 mg/scoop”.
- Revise the following statement (new wording in red, deleted wording in strikethrough):
Each level dosing scoop (b) (4) provides approximately 1g of the oral powder which contains 40 mg of tenofovir disoproxil fumarate, which is equivalent to 33 mg of tenofovir disoproxil.
- Relocate the net quantity statement (i.e. 60 grams per bottle) to the bottom of the label, away from the strength statement.
- Under the Usual Dosage statement, include the following:
Viread oral powder should only be mixed with soft foods. Do not mix with liquids.

Reduced-Strength Tablets

- (b) (4)
use a distinct color for each strength that provides adequate differentiation. (b) (4)
- Relocate the strength statement to immediately follow the dosage form statement as presented below.

Viread
(Tenofovir Disoproxil Fumarate) Tablets
XXX mg
- Relocate the net quantity statement (i.e. 30 tablets) to the bottom of the label, away from the strength statement.
- Delete (b) (4) or replace it with an image of the actual Viread tablet.

Please submit a response to this correspondence by Tuesday, January 3, 2011.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

48 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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/s/

KATHERINE SCHUMANN
12/21/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion
Division of Direct-to-Consumer Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 16, 2011

To: Katherine Schumann, M.S., Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Jessica Fox, PharmD, Regulatory Review Officer
Sheila Ryan, PharmD, Group Leader
Division of Professional Promotion (DPP)

Sheetal Patel, PharmD, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)

Subject: NDA 022577 – Viread (tenofovir disoproxil fumarate) powder
NDA 021356/S-038 – Viread (tenofovir disoproxil fumarate) tablets

As requested in DAVP's consult dated July 7, 2011, DPP and DDTCP have reviewed the Viread prescribing information (PI), patient package insert (PPI), and carton and container labeling, which have been updated to provide dosage recommendations for pediatric patients 2 years and older, to include a new oral powder dosage form, and to include additional tablet strengths.

DPP's comments are provided directly below in the proposed substantially complete version of the PI sent via email by DAVP on December 5, 2011. DPP has no comments on the carton and container labeling at this time.

DDTCP's comments are provided directly below in the proposed substantially complete version of the PPI sent via email by DAVP on December 5, 2011.

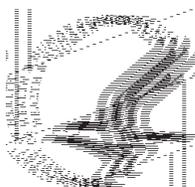
If you have any questions on the PI or carton and container labeling, please contact Jessica Fox at 6-5329 or at Jessica.Fox@fda.hhs.gov. If you have any questions on the PPI, please contact Sheetal Patel at 6-5167 or at Sheetal.Patel@fda.hhs.gov.

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/s/

JESSICA M FOX
12/16/2011

SHEETAL PATEL
12/16/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 22577
21356 S-038

Drug: Viread (tenofovir disoproxil fumarate) oral powder

Date: December 5, 2011

To: Dara Wambach, M.A., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Katherine Schumann, M.S., Regulatory Project Manager, DAVP

Subject: NDA 22577 Viread Oral Powder and NDA 21356 S-038 Viread Tablets –
Comments Regarding Proposed Labeling

Please refer to your New Drug Application (NDA) and supplemental New Drug Application (sNDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD (tenofovir disoproxil fumarate) oral powder and tablets. Also refer to your submission dated November 3, 2011, containing the revised package insert (PI) and patient package insert (PPI) for VIREAD. The following comments regarding Section 8.4, Pediatric Use, are being communicated on behalf of the review team.

1. For your efficacy analysis please include only subjects who were 2 to < 12 yrs of age at enrollment (N=92) and provide a statement explaining that 5 subjects were > 12 yrs of age at enrollment.
2. Please report efficacy results as derived from the "snapshot" analysis.
3. Please include a statement describing number of subjects who discontinued the study prematurely for reasons other than virologic failure/lack of efficacy.
4. Please delete the last sentence regarding excluding missing data.

In recalculating efficacy for the description of the pediatric trial in section 8.4, please consider the following. Two subjects (9044 and 9054) appear to have added a new drug (LPV/r) during the randomization phase and we believe they should be counted as failures instead of successes

according to the snapshot algorithm. Please change this designation or clarify why these two subjects should not be counted as failures.

5. In addition, based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication, we recommend making revisions to Patient Counseling Information and Information for Patients sub-section. These proposed revisions have been modified slightly as compared to suggested revisions sent to you on September 15, 2011.

PATIENT COUNSELING INFORMATION/the second bullet of **Information for Patients** sub-section should be revised as follows:

~~The use of VIREAD has not been shown to reduce the risk of transmission of HIV-1 or HBV to others through sexual contact or blood contamination. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to re-use or share needles.~~

Patients should avoid doing things that can spread HIV-1 or HBV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** Tenofovir is excreted in breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

PATIENT INFORMATION LABELING:

a. The last bulleted paragraph in the section **“What should I tell my healthcare provider before taking VIREAD?/Before you take VIREAD, tell your healthcare provider if you:”** should be revised as follows:

~~• are breast feeding or plan to breast feed. You should not breast feed if you have HIV infection or AIDS. The virus that causes HIV can pass through your breast milk to your baby. It is not known if VIREAD can pass through your breast milk and harm your baby. Talk to your healthcare provider about the best way to feed your baby.~~ **Do not breastfeed.** Tenofovir is excreted in breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

b. The second paragraph in the section **“General information about VIREAD** should be revised as follows:

~~VIREAD does not reduce the risk of passing HIV-1 or HBV to others through sexual contact or blood contamination. Continue to practice safer sex and do not use or share dirty needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or~~

~~razor blades.~~ Avoid doing things that can spread HIV-1 or HBV infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

A shot (vaccine) is available to protect people at risk for becoming infected with HBV.

Additional revisions to Sections 2.1, 2.2, 5.6, 8.3, 8.4 and 12.3 are provided in track changes in the attached PI and PPI.

Please submit a response to this correspondence by Monday, December 12, 2011.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

47 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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/s/

KATHERINE SCHUMANN
12/05/2011



NDA 22-577

INFORMATION REQUEST

Gilead Sciences, Incorporated
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viread® (tenofovir disoproxil fumarate) 40 mg/gram oral powder.

We also refer to your amendment dated November 23, 2011, and have the following comments and information requests. We request your written response by December 8, 2011.

1. We agree with your revised proposed acceptance criteria for degradation products contents at release. With regard to the revised proposed acceptance criteria for degradation products contents during shelf-life, we believe that the proposed acceptance criteria should be based on the results observed during storage of samples at 25°C/60%RH for 36 months, 30°C/65% RH for 24 months, and 40°C/75% RH for 6 months. In the following Table 1, we are proposing the acceptance criteria based on the results.

Table 1: Viread® Oral Powder Stability Study Results and Proposed Acceptance Criteria for Degradation Products during Shelf-life

Deg. Product/ (NMT %) Lot No.	Deg. Product Content at or before 36 Month Time Point (%) 25°C/60% RH	Deg. Product Content at or before 24 Month Time Point (%) 30°C/65% RH	Deg. Product Content at or before 6 Month Time Point (%) 40°C/75% RH	Gilead Proposed Shelf-life Limits (NMT %) in 11/23/11 Amendment	FDA Proposed Shelf-life Limits (NMT %) in 11/30/11 Information Request
Total Degradation Products					

(b) (4)

(b) (4)

2. Your response to Comment 3 in our Information Request letter dated November 15, 2011, did not include supportive information for the statement made in Section 2.4.4.6 of the NDA [REDACTED] (b) (4) [REDACTED] Therefore, please submit a revised statement.

3. We agree with your revised proposed acceptance criterion of $Q = \text{(b)(4)}$ at 60 minutes for the dissolution method for Viread[®] Oral Powder.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Katherine Schumann, Regulatory Project Manager the Office of New Drugs (Katherine.Schumann@fda.hhs.gov).

If you have any questions regarding this CMC letter, call Jeannie David at (301) 796-4247.

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
11/30/2011
Acting Branch Chief



NDA 22-577

INFORMATION REQUEST

Gilead Sciences, Incorporated
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viread® (tenofovir disoproxil fumarate) 40 mg/gram oral powder.

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 written response by November 21, 2011.

- 1) On the basis of the batch analysis and stability data for the Viread® Oral Powder drug product batches, we recommend the following changes to the degradation products contents in the specification for the drug product:

Degradation Product	Gilead Proposed Acceptance Criterion	FDA Recommended Acceptance Criterion
At Release:		
Total Degradation Products (b) (4)		(b) (4)
Each of Any unspecified Degradation Product		
Shelf-Life:		
Total Degradation Products (b) (4)		
Each of any unspecified degradation Product		

- 2) Please provide explanation for the out of specification results observed for the drug product Lot# AD0804B1 when samples were analyzed at the 6 months time point after storage under accelerated conditions (40°C/75% RH).
- 3) In the **Section 2.4.4.6. Qualification of Excipients/Impurities/Degradation Products** of the original NDA submission, you have stated that “The pediatric clinical development program used the intended commercial formulations of the powder and tablet formulations of TDF. All excipients are compendial, used in oral pharmaceuticals at similar levels and considered safe at the maximum human recommended dose. All impurities/degradation products have previously been adequately qualified and appear to be safe for the intended use at the proposed clinical dose.” Please provide supporting documentation showing that the ethylcellulose levels present in the oral pharmaceuticals is similar to the level present in 7.5 scoops of Viread Oral Powder (maximum daily dose) which is equivalent to (b)(4) grams of ethylcellulose.
- 4) Based on the evaluation of the provided dissolution data, we recommend that the dissolution specification for your product be changed to Q=(b)(4) at 45 minutes.

If you have any justification to show that you would not be able to meet these acceptance criteria, include as part of that justification all available dissolution profile data on the three registration batches, including the data from the stability studies.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Katherine Schumann, Regulatory Project Manager the Office of New Drugs (Katherine.Schumann@fda.hhs.gov).

If you have any questions regarding this CMC letter, call Jeannie David at (301) 796-4247.

Sincerely,

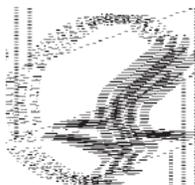
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Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
11/15/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 22577

Drug: Viread (tenofovir disoproxil fumarate) oral powder

Date: November 14, 2011

To: Dara Wambach, M.A., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Katherine Schumann, M.S., Regulatory Project Manager, DAVP

Subject: NDA 22577 Viread Oral Powder Comments regarding Instructions for Use

Please refer to your New Drug Application (NDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD (tenofovir disoproxil fumarate) oral powder. Also refer to your submission dated November 3, 2011, containing the revised Instructions for Use for VIREAD oral powder. The following comments are being communicated on behalf of the review team. These comments are only preliminary and may change at the time of our full review of the PPI and IFU section based on the information in the Substantially Complete PI.

1. Since the IFU will be at the end of the PPI, delete the title and add a bolded section header called "Instructions for Use."
2. Avoid using all capital letters as it may make the information harder to read and may give the appearance of shouting at the reader.
3. All figures should be placed adjacent to the appropriate text and labeled sequentially, such as Figure A, Figure B, etc. Reference each figure in the text as for example "See Figure A."
4. In the Introductory paragraph, change [REDACTED] ^{(b)(4)} to "Instructions for Use."
5. After the introductory paragraph "Read the Instructions for Use..." add a header called "Important Information."

6. The statement “Viread oral powder comes in a box...” should become the first bullet under the new header, followed by the figure of the scoop. Reference the figure, and label the figure as discussed above.
7. Add a 4th bullet as follows: “Give the entire dose right away after mixing to avoid a bad taste. Please reinsert information about poor palatability of mixture if not taken immediately in the PI.
8. Under to “To prepare and give the medicine”
 - Delete (b) (4) and leave the first statement as “Wash and dry your hands.”
 - Clarify in instruction 1 whether this should state “press down and turn.” Add a figure to show this step and provide more descriptive language regarding peeling off the foil seal, such as “pull tab to open” or other instruction as appropriate. Label and reference the figures as stated above.
 - Add a figure to step 3 showing how to use the flat edge of knife to make the powder even with the top of the dosing scoop.
 - The line and “1/2” mark are not easily visualized on the dosing scoop. Consider adding color to make this more readily visible.
 - Under step 4, revise the second statement to match the statement that is now the 4th bullet under “Important information”: “Give the entire dose right away after mixing to avoid a bad taste.
 - Delete the header (b) (4) The next 2 bullets should be a continuation of the instructions above, and numbered 5 and 6.
 - Delete the last bullet and instead add a section called “How should I store Viread?” Copy and paste the storage information from the “How should I store Viread?” section of the PPI.

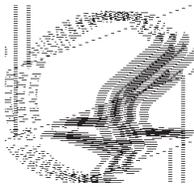
Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
11/15/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 22577

Drug: Viread (tenofovir disoproxil fumarate) oral powder

Date: October 4, 2011

To: Dara Wambach, M.A., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Katherine Schumann, M.S.

Subject: NDA 22577 Viread Oral Powder Request for Information

Please refer to your New Drug Application (NDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD (tenofovir disoproxil fumarate) oral powder.

1. The currently proposed draft labeling does not contain detailed instructions for patients/caregivers regarding the measurement of one half scoop and one full scoop of the powder. We recommend additional "Instructions for Use" to be included at the end of the Patient Package Insert. These instructions could include diagrams showing appropriate measuring for a half scoop and a full scoop of powder. They could also provide a more detailed description of what food items may be used as vehicle for the powder and any foods that should NOT be used as vehicle and optimal time limits for mixing and dosing. Instructions should be based on stability or palatability studies or practices followed during the clinical trial. These Instructions for Use are intended for patients/caregivers and should be in consumer-friendly language. Consider revising the bottle and carton labels to include, "See Patient Package Insert for instructions on use of the dosing scoop."
2. In order to validate that the Instructions for Use are adequate you may wish to consider performing a simulated use study or label comprehension assessment with representative users.

Please resubmit labeling addressing the above comments by Thursday, October 13, 2011.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

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/s/

ELIZABETH G THOMPSON
10/04/2011
Elizabeth Thompson for Katie Schumann

David, Jeannie C

From: David, Jeannie C
Sent: Monday, September 26, 2011 5:17 PM
To: 'Rebecca Mock'; Dawne Hom
Cc: Regulatory Archives; Schumann, Katherine
Subject: RE: NDA 22-577, Viread (tenofovir DF) 40 mg/g Oral Powder, clarification on information request

Dear Rebecca and Dawne,

Please see our responses in blue below.

Regards,

Jeannie

Jeannie David, MS
Regulatory Health Project Manager
CDER/OPS/ONDQA
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 1475
Silver Spring, MD 20993
Phone: (301) 796-4247
Fax: (301) 796-9877
jeannie.david@fda.hhs.gov

From: Rebecca Mock [mailto:Rebecca.Mock@gilead.com]
Sent: Tuesday, September 20, 2011 10:16 AM
To: David, Jeannie C
Cc: Regulatory Archives; Dawne Hom
Subject: NDA 22-577, Viread (tenofovir DF) 40 mg/g Oral Powder, clarification on information request

Dear Jeannie,
Follow-up to my voice mail. Could we get clarification on question 5 on the information request dated 16 Sept 2011 for NDA 22-577?

5) Please provide 2 samples of the Viread Oral Powder drug product package along with the dosing scoop and instructions for dosing that include one full scoop and one half scoop measurement.

- **Are you requesting product in the primary container closure system?**

Yes, we are requesting the drug product in the intended commercial container/closure system. Since the proposed container/closure system does not include secondary packaging in a carton, we also want to know how the scoop will be packaged and delivered to the consumer.

- **We just provided 3 commercial image scoops to Katherine Schumann last week. Do you**

need additional commercial scoops? This may be problematic because we had only prototypes of the commercial scoop and we sent them to the agency already.

We request samples of the final to-be-marketed scoop as soon as possible. If these are not readily available, describe how the prototype differs from the final to-be-marketed scoop.

- The draft labeling (Section 1.14.1.3 of the NDA) contains instruction on dosing. Is that what you are requesting?

The currently proposed draft labeling does not contain detailed instructions regarding the measurement of one half scoop and one full scoop of the powder. Please provide this information for review, and once found acceptable, we may request to include this in the revised labeling.

Thanks much for your help in clarifying this request.

Kind regards,
Rebecca Mock

Rebecca Mock
Associate Director, Regulatory Affairs
650-372-7041

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/s/

JEANNIE C DAVID
09/26/2011



NDA 22-577

INFORMATION REQUEST

Gilead Sciences, Incorporated
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viread[®] (tenofovir disoproxil fumarate) 40 mg/gram oral powder.

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 written response by September 27, 2011.

- 1) We noticed the following observations when the NDA registration stability batches were stored:
 - a) At the 6 months time point, the strength of the drug product was decreased by (b) (4) to (b) (4) when stored at 25°C/60%RH and (b) (4) to (b) (4) when stored at 30°C/65%RH but the Total Degradation Products content increased by (b) (4) only (at 25°C/60%RH) and (b) (4) to (b) (4) only (at 30°C/65%RH), respectively.
 - b) At the 24 months time point, the strength of the drug product was decreased by (b) (4) to (b) (4) when stored at 25°C/60%RH and (b) (4) to (b) (4) when stored at 30°C/65%RH but the Total Degradation Products content increased by (b) (4) to (b) (4) only (at 25°C/60%RH) and (b) (4) to (b) (4) only (at 30°C/65%RH), respectively.
 - c) At the 36 months time point, the strength of the drug product was decreased by (b) (4) to (b) (4) when stored at 25°C/60%RH but the Total Degradation Products content increased by (b) (4) to (b) (4) only.
 - d) Under the accelerated conditions (40°C/75%RH), at the 6 months time point the strength of the drug product significantly decreased by (b) (4) to (b) (4) but the Total Degradation Products content increased by (b) (4) to (b) (4) only.

Please provide explanation for the above discrepancies.

- 2) Please provide the stability data analysis and results for any other drug product batches (preclinical, clinical, and intended commercial) that are available.
- 3) If there is any interaction between the tenofovir disoproxil fumarate active ingredient and/or degradation products and ethylcellulose or any other excipients, please investigate and provide the results.
- 4) Please provide results of the compatibility studies that were conducted between the tenofovir DF drug substance and ethylcellulose under various pH, temperature, and humidity conditions.
- 5) Please provide 2 samples of the Viread Oral Powder drug product package along with the dosing scoop and instructions for dosing that include one full scoop and one half scoop measurement.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Katherine Schumann, Regulatory Project Manager the Office of New Drugs (Katherine.Schumann@fda.hhs.gov).

If you have any questions regarding this CMC letter, call Jeannie David at (301) 796-4247.

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/

RAPTI D MADURAWA
09/16/2011

From: [Schumann, Katherine](#)
To: [Dara Wambach](#);
cc: ["Erik Berglund"](#);
Subject: NDA 22577 Viread Oral Powder - Request for Scoop Samples
Date: Monday, September 12, 2011 2:20:42 PM

Dara,

DMEPA would like to see samples of the Viread Oral Powder dosing scoop as part of the NDA 22577 review. Could you have several scoops sent directly to my attention at your earliest convenience? I was not given an exact number, but I think 3 would be fine.

Please let me know if you have any questions.

Warm Regards,

Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6237
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
09/12/2011

From: [Schumann, Katherine](#)
To: [Dara Wambach](#);
Subject: Tenofovir - Pediatric Exclusivity Determination
Date: Tuesday, September 06, 2011 3:36:26 PM

Dear Dara,

Please find below your notification regarding the pediatric exclusivity determination for Viread (tenofovir):

Pediatric Exclusivity has been granted for studies conducted on tenofovir, effective September 6, 2011, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a), as amended by the Best Pharmaceuticals for Children Act (BPCA). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book. For additional information, please see the Guidance for Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080558.pdf>).

In accordance with section 505A(e)(1) of the Act, as amended by FDAAA (Pub. L. No. 110-85), approved drugs for which a pediatric exclusivity determination was made, on or after September 27, 2007, shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, we remind you that section 17 of the BPCA, as reauthorized and amended under the FDA Amendments Act of 2007, requires for one year after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Please let me know if you have any questions.

Warm Regards,

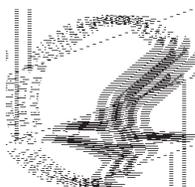
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6237
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
09/07/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: 22577

Drug: Viread (tenofovir disoproxil fumarate) oral powder

Date: August 23, 2011

To: Dara Wambach, M.A., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Tafadzwa Vargas-Kasambira, M.D., M.P.H., Clinical Reviewer
Linda Lewis, M.D., Clinical Team Leader

Subject: NDA 22577 Viread Oral Powder Request for Information

Please refer to your New Drug Application (NDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD (tenofovir disoproxil fumarate) oral powder.

We reference the Table on Page 9 of your Annotated Written Request, that lists the trials submitted in support of your pediatric pharmacokinetic development program. In order to assist the Pediatric Exclusivity Board in making a determination on your eligibility for this designation, please revise this Table to summarize the total number of subjects evaluated in all pediatric PK studies according to the age categories specified in the Written Request i.e. 2 years to < 6 years, 6 years to < 12 years, and 12 years to 18 years. Please send the updated Table to us via email, as a separate Addendum by Friday, August 26, 2011; there is no need to resend the entire Annotated Written Request.

Please contact me at 301-796-1182 if you have any questions regarding the contents of this transmission.

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
08/23/2011



NDA 22577

FILING COMMUNICATION

Gilead Sciences, Incorporated
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your New Drug Application (NDA) dated June 16, 2011, received July 18, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Viread[®] (tenofovir disoproxil fumarate) 40 mg/gram oral powder.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is January 18, 2012.

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, midcycle, 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 December 28, 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 supplemental application and is not indicative of deficiencies that may be identified during our review.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the partial deferral granted on March 8, 2006, for the pediatric study requirement for this application for pediatric patients birth to less than 2 years of age.

We note that you have submitted pediatric studies with this application for pediatric patients 2 to less than 12 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

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/s/

JEFFREY S MURRAY
08/22/2011



NDA 22577

**NDA ACKNOWLEDGEMENT
USER FEES RECEIVED**

Gilead Sciences, Incorporated
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Viread[®] (tenofovir disoproxil fumarate) 40 mg/gram oral powder.

You were notified in our letter dated July 14, 2011, that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received all required fees and your application has been accepted as of July 18, 2011.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 16, 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number cited above should be included 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

If you have any questions, contact Katherine Schumann, Regulatory Project Manager, at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Victoria Tyson
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

VICTORIA L TYSON
07/20/2011



IND 52,849

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Viread[®] (tenofovir disoproxil fumarate).

We also refer to the teleconference between representatives of your firm and the FDA held on June 15, 2011. The purpose of the meeting was to discuss your planned submission of a new pediatric NDA (Viread[®] Oral Powder) and a supplement for reduced-strength tablets (150, 200 and 250 mg strength tablets of Viread[®]) for the treatment of HIV-1 infection in pediatrics.

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

If you have any questions, call me at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Drug Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Pre-NDA

Meeting Date and Time: June 15, 2011 1:30 PM – 3:00 PM
Meeting Location: Teleconference

Application Number: 52,849
Product Name: Viread® (tenofovir disoproxil fumarate)
Indication:
Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Linda Lewis, M.D.
Meeting Recorder: Katherine Schumann, M.S.

FDA ATTENDEES

1. Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
2. Linda Lewis, M.D., Clinical Team Leader, DAVP
3. Tafadzwa Vargan-Kasambira, M.D., M.P.H., Medical Officer, DAVP
4. Sarah Robertson, Pharm D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
5. Shirley Seo, Ph.D., Clinical Pharmacology Reviewer, OCP
6. Rao Kambhampati, Ph.D., Product Quality Reviewer, ONDQA
7. Angelica Dorantes, Ph.D., Biopharmaceutics Team Leader, ONDQA
8. Benjamin Ortiz, M.D., Clinical Reviewer, Office of Pediatric Therapeutics (OPT)
9. Victoria Tyson, Chief, Project Management Staff, DAVP
10. Katherine Schumann, Regulatory Project Manager, DAVP

SPONSOR ATTENDEES

1. Andrew Cheng, M.D., Ph.D., SVP HIV Therapeutics and Development Operations
2. Erin Quirk, M.D., Senior Director, HIV Clinical Research
3. Thomas Weber, Ph.D., VP Analytical and Quality Operations
4. Jodi Fausnaugh-Pollitt, Director, Analytical Chemistry
5. Michael Wulfsohn, M.D., VP, Biometrics
6. Shan-Shan Chen, MPH, Senior Director, Biometrics
7. Brian Kearney, PharmD, Senior Director, Clinical Research (Pharmacology)
8. David Pizzuti, M.D., VP Regulatory Affairs
9. Pamela Danagher, M.Sc., Senior Director, Regulatory Affairs
10. Sujatha Narayan, Director, CMC Regulatory Affairs
11. Dara Wambach, M.A., Associate Director, Regulatory Affairs

1.0 BACKGROUND

Gilead Sciences, Inc. (Gilead) is planning to submit a new pediatric NDA for Viread[®] (tenofovir disoproxil fumarate) Oral Powder and a supplemental NDA for reduced-strength Viread tablets (150 mg, 200 mg, and 250 mg). The sponsor's pediatric clinical trials using tenofovir DF were conducted to address the Division's Pediatric Written Request of December 21, 2011, as amended.

An earlier Type B, pre-NDA meeting was held on April 29, 2010, to discuss the results of clinical trial GS-US-104-0352 and the submission of an NDA for Viread[®] oral powder. During this meeting, the Division suggested that Gilead consider developing a reduced-strength tablet to address potential non-adherence issues with dosing of the oral powder, particularly in older, larger children who would require more of the medication to achieve appropriate drug exposure.

Gilead followed this meeting with a proposal (dated July 14, 2010) to develop reduced-strength tablets for patients weighing 17 to less than 35 kg, and to submit a request for biowaver in lieu of an *in vivo* bioequivalence study. DAVP provided written advice on August 19, 2010 in which agreement with the proposal was expressed.

On March 30, 2011, Gilead submitted a request for an additional pre-NDA meeting to discuss their plans for concurrent submission of the new Viread[®] oral powder NDA and supplemental NDA for reduced-strength tablets, in response to the Pediatric Written Request. The Division provided preliminary responses to Gilead's questions on June 13, 2011.

2. DISCUSSION

Questions submitted by the Sponsor are in **bold**, the Agency's preliminary comments are in *italics*, and discussions during the June 15, 2011 meeting are in regular font.

Question 1: Does the Agency agree with Gilead's plan for submission of the following applications:

a) a new NDA for tenofovir DF oral powder, supported by data from study GS-US-104-0352, and

b) a sNDA to introduce the reduced-strength tenofovir DF tablets, supported by a request for biowaiver, will fulfill the terms of the Pediatric Written Request for Viread and secure Pediatric Exclusivity?

Your plan to submit a new NDA for tenofovir DF oral powder, and to submit an sNDA to introduce the reduced-strength tenofovir DF tablets, is acceptable.

Please include in your sNDA the following information/data supporting the biowaiver request for the reduced 150, 200, and 250 mg strengths of tenofovir DF tablets; 1) a brief summary of the PK (bioavailability) data available for the approved 300 mg tablet; 2) a comparative table

showing that the compositions of the 150, 200, and 250 mg strengths are proportionally similar to the composition of the approved 300 mg strength tablet; and 3) comparative multi-point dissolution profile data (n=12) for all the strengths at pH 1.2, 4.5, and 6.8 using the same dissolution testing conditions (i.e., USP 2, 50 rpm). For the estimation of the similarity f_2 values, the approved 300 mg tenofovir tablet should be used as the reference.

We remind you that the report for the proposed dissolution method as well as the data supporting the proposed dissolution specification should also be included in the sNDA submission.

The Review Team provides advice to the Pediatric Exclusivity Board on whether you have adequately met the terms of the Pediatric Written request, but is unable to advise you on whether your submission of the NDA and sNDA will secure Pediatric Exclusivity. Exclusivity determinations are made solely by the Pediatric Exclusivity Board.

Meeting Discussion:

Gilead asked the Division to clarify the contents of the requested “brief summary of PK (bioavailability) data.” Dr. Lewis replied that DAVP expects a very brief overview of PK information on the approved Viread[®] tablet, which could be as short as half a page. Gilead replied that this brief summary will be provided in the sNDA.

Dr. Weber of Gilead then asked the FDA to clarify the request for comparative multi-point dissolution profile data using specific testing conditions (USP 2, 50 rpm), as this was not a planned component of the sNDA. Dr. Weber also explained that Gilead does not believe a dissolution profile comparison as a function of pH would be meaningful, as data suggest that ^{(b) (4)} of the tablet dissolves within 15 minutes.

Dr. Dorantes replied that this information is necessary, as Gilead’s dissolution method (2 per cent surfactant, 100 revolutions/min) is not sufficiently discriminatory. Dr. Weber replied that Gilead modified their dissolution testing methods since the last meeting with the Agency in August, 2010, and clarified that the current methods do conform to the Agency’s recommendations (USP 2, 50 rpm, no surfactant). Dr. Dorantes agreed that if the new testing methodology had been implemented, then the additional requested data would not be necessary.

Question 2: Could the Agency please confirm its agreement with the timing of submission of the original NDA and sNDA 1 month prior to the availability of the 6 month reduced-strength tablet stability data and comment on whether a 6-month or 10-month review period should be anticipated?

We agree with your plan to submit the original NDA and sNDA one month prior to the availability of the 6-month reduced-strength tablet stability data. Please provide an outline the stability package that will support the oral powder NDA, and indicate the amount of stability data which will be included with the submissions.

We anticipate that both the NDA and the sNDA will be reviewed within the same 6-month review period, as the sNDA is being submitted in response to the Pediatric Written Request.

Meeting Discussion:

Gilead explained that the oral powder NDA will contain primarily summary information on the drug substance, because they plan to cross-reference information contained in DMF (b) (4) to provide most of the data, including manufacturing information. Gilead confirmed that the oral powder NDA will contain specifications and analytical methods.

Question 3: Does the Agency have any additional comments or requests regarding the proposed content and format of the NDA and sNDA?

Product Quality:

1. *It is acceptable to cross-reference the drug substance CMC information to the Viread[®] Tablet NDA 21356, and Viread[®] Oral Powder CMC information to the DMF (b) (4) however, in the NDA and sNDA submissions, please provide exact hyperlinks to the appropriate information.*

Meeting Discussion:

Gilead explained that it will not be possible to cross-reference page numbers or hyperlink to the referenced DMF, because the DMF is not owned by Gilead and the information is proprietary. Dr. Kambhampati replied that this is acceptable, and suggested the sponsor provide summaries of the key sections, such as specifications, components and composition and batch analysis, in the NDA.

Clinical:

2. *Please submit mock safety datasets, as well as the corresponding define.pdf files, prior to submission of your Viread[®] pediatric NDA and sNDA.*

Meeting Discussion:

Gilead explained that the actual safety datasets have already been prepared and are ready to be submitted. Gilead confirmed that the prepared datasets are very similar to those submitted in a recent pediatric efficacy supplement to Viread[®] NDA 21356 (for ages 12 to 18). Therefore, they should be in a format acceptable for review. DAVP agreed that it would be acceptable for Gilead to submit the prepared datasets to the new NDA without first submitting mock datasets.

3. *Your plan to submit the same Safety Update Report to the new NDA and the sNDA is acceptable; however, as we anticipate a priority review timeline, we request SUR*

submission 3 months following the initial submissions to allow adequate time to review the data.

Meeting Discussion:

Gilead confirmed that a Safety Update Report would be submitted 3 months after the initial NDA.

Clinical Pharmacology:

- 4. When the NDA and sNDA are submitted, DSI inspections will be requested for the highest enrolling PK site(s) and the bioanalytical site for the clinical study (GS-US-104-352), as well as the clinical and bioanalytical sites for the BE study (GS-US-104-312). In order to allow us to better prepare, please provide information regarding which study sites enrolled PK subjects in your clinical study (GS-US-104-352) along with subject numbers at each site.*

Meeting Discussion:

Gilead agreed to provide additional information on the PK, clinical and bioanalytical sites as requested.

DAVP ended the meeting by explaining that although the Division does not foresee any issues with the sponsor's request for pediatric exclusivity, the final decision will be made by the Exclusivity Board. The Division also reminded the sponsor of previously-raised concerns regarding the failure of the pivotal trial to achieve its primary efficacy endpoint. DAVP further stated that it is possible to be granted pediatric exclusivity without approval for the proposed pediatric indication, should the reviewed data lead to such a conclusion. The Division asked Gilead to submit an annotated Written Request in the request for Exclusivity.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

At the conclusion of the meeting, there were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Gilead will provide additional information on the PK and bioanalytical sites for trial GS-US-104-352 and the clinical and bioanalytical sites for BE trial GS-US-104-312.	Gilead	As soon as possible
Gilead will submit a new NDA for Viread® oral	Gilead	As soon as possible

powder and a supplement to NDA 21356 for reduced-strength Viread® tablets.		
Gilead will include an annotated WR	Gilead	With the NDA

6.0 ATTACHMENTS AND HANDOUTS

Attached is a slide presentation provided by the sponsor, dated June 15, 2011, in response to FDA's preliminary comments of June 13, 2011.

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/s/

DEBRA B BIRNKRANT
07/15/2011



NDA 22577

UNACCEPTABLE FOR FILING

Gilead Sciences, Incorporated
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

We have received your new drug application (NDA) submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Viread® (tenofovir disoproxil fumarate) 40 mg/gram oral powder

Date of Application: June 16, 2011

Date of Receipt: June 16, 2011

Our Reference Number: NDA 22577

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number for the unpaid fees and the summary portion of the invoice with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

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

If you wish to send payment by wire transfer, or if you have any other user fee questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions, contact Kathleen Schumann, M.S., Regulatory Project Manager, at (301) 796-1182 or the Divisions main number (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Victoria Tyson
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

VICTORIA L TYSON
07/14/2011



NDA 22577

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc.
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

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: VIREAD[®] (tenofovir disoproxil fumarate) oral powder

Date of Application: June 16, 2011

Date of Receipt: June 16, 2011

Our Reference Number: NDA 22577

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 August 15, 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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 me at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Katherine Schumann, M.S.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

KATHERINE SCHUMANN
06/28/2011

From: [Schumann, Katherine](#)
To: ["Dara Wambach";](#)
Subject: NDA 22577 Viread oral powder investigator and facilities information
Date: Monday, June 20, 2011 4:06:03 PM

Dear Dara,

As mentioned during the pre-NDA meeting, the Division will be requesting inspections as part of the review of NDA 22577. I am writing to request and confirm certain information that will be needed for this purpose.

First, I'd like to confirm that the contact information below for Drs. Lagen and Saez-Llorens is correct. If possible, could you also provide an email address for Dr. Lagen and a fax number for Dr. Saez-Llorens (if available)?

Study GS-US-104-0312

Thomas H. Lagen, MD
Northwest Kinetics, Inc.
3615 Pacific Avenue,
Tacoma, WA 98418, USA
Phone: +1 (253) 593-5304 x379
Fax: +1 (253) 593-5181

Study GS-US-104-0352

Dr Xavier Sáez-Llorens
Hospital Del Niño,
Avenida Balboa, Street 34
Panama City, Panama 5-4087
Tel. 507-512-9808 ext.174
xsaezll@cwpanama.net
xsaezll@gmail.com

Second, I'd like to communicate the following request from the clinical pharmacology team:

Please submit a list of bioanalytical sites with addresses used for analysis of PK blood samples in studies US-GS-104-0352 and US-GS-104-0312. Please also provide a point of contact and phone

number for each site.

I know that clinical laboratory facilities are listed on the Forms 1572, but contact names and phone numbers were not included on those that I referenced. We would appreciate very much if you could provide this additional information.

Please let me know if you have any questions.

Warm Regards,

Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6237
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
06/20/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 52,849

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Dara Wambach, M.A.
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Viread[®] Oral Powder (tenofovir disoproxil fumarate).

We also refer to the meeting between representatives of your firm and the FDA on April 29, 2010. The purpose of the meeting was to discuss the pediatric NDA for Viread[®] Oral Powder (tenofovir disoproxil fumarate) for HIV-1 infection planned for submission September 2010.

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

If you have any questions, call Carrie Ceresa, Pharm D., MPH at (301) 796-4108.

Sincerely,

{See appended electronic signature page}

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

Enclosure



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 29, 2010, 2:00- 3:30 pm
Meeting Location: White Oak, Building 22, Room 1309

Application Number: IND 52,849
Product Name: Viread® (tenofovir disoproxil fumarate)
Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Linda Lewis, M.D., Medical Team Leader
Meeting Recorder: Carrie Ceresa, Pharm D., MPH, Regulatory Project Manager

FDA ATTENDEES

Debra Birnkrant, M.D.	Director
Jeff Murray, M.D., MPH	Deputy Director
Linda Lewis, M.D.	Medical Team Leader
Rebecca Levorson, M.D.	Medical Officer
Julian O'Rear, Ph.D.	Clinical Virology Team Leader
Narayana Battula, Ph.D.	Clinical Virology Reviewer
Sarah Robertson, Pharm D.	Clinical Pharmacology Team Leader
Shirley Lu, Ph.D.	Clinical Pharmacology Reviewer
Greg Soon, Ph.D.	Biometrics Team Leader
Karen Qi, Ph.D.	Biometrics Reviewer
Steve Miller, Ph.D.	Acting Branch Chief, ONDQA
Shrikant Pagay, Ph.D.	Product Quality Reviewer, ONDQA
Russ Fleischer, PA-C, MPH	Senior Clinical Analyst
Yodit Belew, M.D.	Medical Officer
Victoria Tyson	Chief, Project Management Staff
Carrie Ceresa, Pharm D.	Regulatory Project Manager
Susan Cummins, M.D., MPH	Senior Science Advisor, PMHS
Denise Pico-Branco	Senior Regulatory Health Project Manager, PMHS
Kristina Toliver	Team Leader, DMEPA
Lori Cantin, Pharm D.	Safety Evaluator, DMEPA
Twanda Scales	Safety, Regulatory Project Manager, OSE

SPONSOR ATTENDEES

Shan-Shan Chen, MPH	Senior Director, Biometrics
Steve Chuck, M.D.	Vice President, HIV Therapeutics
Pamela Danagher, M.Sc.	Senior Director, Regulatory Affairs
Brian Kearney, Pharm D.	Senior Director, Clinical Research (Clinical Pharmacology)
Dara Wambach, M.A.	Associate Director, Regulatory Affairs
David Warren, M.D.	Associate Director, Clinical Research

1.0 BACKGROUND

The purpose of this Pre-NDA meeting was to discuss the results from the clinical trial in pediatric subjects ages 2 to 12 (Study GS-US-104-0352) that will be submitted to support the treatment of HIV-1 infection in children 2-12 years of age with Viread tablets and an oral powder. In addition, this meeting was held to discuss the requirements of the Pediatric Written Request and PREA postmarketing commitments for Viread.

2.0 DISCUSSION

- 1. Does the Agency agree that Gilead has identified an appropriate dose (i.e., 8 mg/kg) of Viread for use in HIV-1 infected children 2 to 12 years of age, with respect to its plans to fulfill the Pediatric Written Request for Viread and secure Pediatric Exclusivity?**

Exclusivity determinations are made solely by the Pediatric Exclusivity Board; the review team is not able to advise you as to whether your pediatric studies to date fairly fulfill the terms of the Pediatric Written Request and will secure Pediatric Exclusivity for Viread. The review team provides technical advice to the Exclusivity Board regarding whether you have fairly met the terms of the Written Request. We remain concerned that Study 352 failed to achieve its efficacy endpoints but we have not reviewed all the data and do not have a fully satisfactory explanation of the results. The Exclusivity Board takes into consideration whether you have made a good effort to meet the terms of the Written Request, even if a study fails in some critical aspect.

We acknowledge that the exposures from pediatric Studies 926 and 927, following administration with a 75-mg tablet, were not significantly different from adult exposures resulting from a 300-mg daily dose. An 8 mg/kg dose for pediatric patients appeared reasonable to achieve effective adult exposures based on these pharmacokinetic studies using the 75-mg tablet.

Your Pediatric Written Request requires use of an age-appropriate formulation for your pediatric studies, along with an appropriate dose. Once a pediatric patient is developmentally capable of swallowing a tablet (generally those who are 6 years and older), tablet dosing is the age-appropriate formulation because it provides more reliable dosing. Upon review of your briefing document and the summary of Study 352, it is uncertain that an appropriate formulation was identified for all age groups. We are concerned that the entire dose of Viread powder may not have been consumed by some subjects, given the volume of powder required to adequately dose heavier pediatric subjects and the relatively lower exposure observed in this study relative to historical pediatric PK studies. In particular, children ages 6 to <12 years had lower exposure than would have been expected based on previous data with the 75-mg tablet. The difference in exposures was larger in older children than for the younger children (who were not required to use as much

powder to prepare an appropriate dose), further supporting our concerns. Please provide any records (e.g., diaries, etc) that documented the administration of doses at home and in the clinic on PK sampling days in Study 352.

Discussion

Gilead asked the DAVP to clarify whether the 8 mg/kg dose is appropriate for all pediatric patients ages 2 to 12. The DAVP responded that based on the results of the two studies with the 75 mg tablet, the 8 mg/kg dose appears appropriate. The DAVP reiterated concerns with the powder formulation and are trying to determine why the study failed and informed Gilead, that based on the data with the 75 mg tablets, the results are disappointing. That is, we would have expected to see the PK match that of adults more closely using the 8 mg/kg dose. Gilead referred to the Guidance on extrapolation of efficacy data in HIV-1. The DAVP explained that this was done for the adolescent study. The DAVP informed Gilead that when all of the data are submitted and reviewed in more detail we may be able to explain why the study did not demonstrate efficacy.

- 2. Assuming the Agency agrees with the identified dose (see question 1 above), do the safety (as provided) and efficacy data included for Study GS-US-104-0352 support the filing of an NDA for this age group?**

There are likely adequate data for filing but whether there are adequate data for an approval is a review issue and will be determined during that process. However, as mentioned in the July 30, 2009, Pre-NDA meeting, Study 352 failed to meet the primary efficacy endpoint and also did not achieve optimal tenofovir exposure in pediatric subjects, particularly those 6 to < 12 years of age. The summary data do not provide adequate information to be certain that the appropriate dose and formulation have been identified across the entire age range.

Discussion

Gilead explained that they are hesitant to move forward with the NDA because it may not fulfill the Written Request. The DAVP explained that the Exclusivity Board will make that determination.

The DAVP explained that we had high expectations that the oral powder would be successful and were surprised with the outcome and that is why we requested a sample of the formulation. Larger children need to take a fairly large amount of the powder. If the dosing preparation (a mixture of the full dose of the powder with applesauce) is consumed immediately, the oral powder is tasteless but the consistency is gritty like sand, and after about five minutes the unpleasant taste of the medication becomes very apparent. This may explain the lower exposures and potentially lower efficacy in the older children over the longer term. This was not a concern in the smaller pilot study which used the 75 mg tablet.

The DAVP asked Gilead if there were any diaries or administration records for the 0352 Study. Gilead has the time of the dose for PK sampling, but diaries or records were not kept by the subjects enrolled in the trial or their caregivers. Compliance for drug administration on the day of intensive PK sampling in the clinic was also not recorded.

Gilead asked if we can explain why the study failed. The DAVP informed Gilead that this is not the first time a switch study failed. Gilead asked if the results of Study 0352 would support an indication for the treatment of pediatric patients 2-6 years of age. This is a review issue and cannot be addressed without reviewing the data. Gilead asked if our main concern was based on the exposures. The DAVP is concerned with the exposure, efficacy, and maintaining adherence with the oral powder. Together, both the PK data and efficacy data raised questions about potential compliance issues.

The DAVP ask Gilead about their plans to develop pediatric formulations for Truvada and Atripla. Gilead has not discussed this issue as of yet. The DAVP has PK, BE, and safety data on the 75 mg tablets and suggested reintroducing the 75 mg tablet and developing a scored 75 mg tablet. The pediatric powder appears to be appropriate for younger children and a smaller-sized tablet may be useful for other ages as older children can swallow pills. Gilead (b) (4) developed the powder to achieve optimal dosing. (b) (4) (b) (4)

Gilead explained that when they entered into the study they believed that the oral powder was acceptable across the 2 to 12 age range and they understand that the study would need a regulatory review in order to get a final decision. Gilead will discuss treating patients 2 to 6 years of age with the powder formulation and (b) (4)

(b) (4) Gilead asked if the data from Study 0352 would be acceptable for filing with supportive data from Studies 926 and 927. The DAVP explained that we are able to extrapolate efficacy based on PK. Depending on how tightly the doses can be titrated using the tablet, the DAVP clarified that additional safety data to cover doses above 8 mg/kg may be needed if some weight bands significantly exceeded the 8 mg/kg dose.

The DAVP asked Gilead to provide an explanation for the higher exposures observed in studies in which median tablet doses of 5 and 7 mg/kg doses were administered.

The timeline of the Written Request for pediatrics patients 2 to 12 years of age was extended to September, 2010, and Gilead asked about the information required to amend the WR. The DAVP advised Gilead to submit a request to amend the WR by including the 75 mg tablet and Studies 926 and 927. Upper management makes the final decision on amended WRs and the Exclusivity Board makes the final determination on whether pediatric studies fulfill the WR. As stated earlier the Exclusivity Board evaluates the terms of the WR and recognizes that sometimes studies fail. In addition, we have seen products that meet the terms of the WR but do not get approved. The DAVP explained that there are very good qualities to the oral powder and asked Gilead to submit the request to revise the WR at least a month in advance of the September deadline.

(b) (4)



Gilead asked if they could amend the WR after submitting the data from Study 0352. The DAVP responded no, by law when the data from Study 0352 are submitted the request for exclusivity is reviewed. In order to fulfill the terms of a WR, the request for exclusivity must be made at the time the last clinical data are submitted for review; the request for exclusivity can not be made in reference to previously submitted data alone but must be attached to some data not previously submitted.

Gilead asked if the data support a sufficient evaluation of the 8 mg/kg dose. The DAVP responded, yes, but the decision would not be based on the data from Study 0352 alone.

Gilead stated that they provided PK and exposure data from Study 0352 and asked DAVP's opinion about an exposure/response relationship. The DAVP stated that although lower exposures did not appear to have a direct correlation with lower efficacy based on the summary information contained in the background package, the PK substudy was conducted on one day out of the entire 48 weeks of treatment. It is unknown how well the exposures resulting from measurement on one day at week 4 correlate with the overall measure of efficacy at week 48. It is possible that the rate of non-compliance rose between week 4 and week 48 due to the volume of powder that patients were required to take on a daily basis, thus leading to lower exposures over long-term dosing that was not captured at week 4. The 8 mg/kg dose may be acceptable, but the DAVP is concerned that the study did not meet its primary endpoint. The DAVP asked if efficacy data are available comparing the age groups. Gilead responded that they do have subgroup comparisons by age but the population is small. The DAVP expressed that we have concerns about the population and are not sure whether the data will offset these concerns. Gilead explained that 64 patients were purely on powder and 16 patients were on the powder and then switched to the tablet as they got older. The DAVP explained that the group on the combination may be interesting to review to see what changes are apparent when the switch was made from powder to tablet. Gilead explained that if patients tolerated the powder the difference between the age groups may be explained by the number of discontinued patients.

The DAVP asked if data are available regarding how many batches of the powder were made and Gilead responded that they will provide information on additional lots.

3. Does the Agency have any requests for specific analyses for inclusion in the integrated summaries or comments on the proposed content and format of the NDA and 120-Day Safety Update?

- Please provide serum calcium values and calcium values corrected for albumin.*
- Please provide baseline, sequential and changes from baseline in height and weight as raw numbers and also as growth percentiles per appropriate demographic growth charts (e.g., CDC growth charts for US population).*
- Please revise all tables displaying the disposition of study subjects to separate the reason for early discontinuations specifically in regards to the category "safety, tolerability, or efficacy reasons" and provide the specific reason for discontinuation.*

- *Please perform the snapshot analysis for the proportion of patients achieving HIV-1 RNA <400 copies/mL and the proportion of patients achieving HIV-1 RNA <50 copies/mL and provide the relevant data.*
- *Please provide an analysis of efficacy excluding any patients who received the maximum allowed dose (300 mg) when this dose was less than 8 mg/kg.*

3.0 ISSUES REQUIRING FURTHER DISCUSSION

(b) (4)



4.0 ACTION ITEMS

- Gilend will include lot information regarding the batches used for the oral powder.

5.0 ATTACHMENTS AND HANDOUTS

There were no handouts or attachments for this meeting.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-52849

GI-1

GILEAD SCIENCES PMPA
INC

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

/s/

JEFFREY S MURRAY
05/20/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 52,849

MEETING MINUTES

Gilead Sciences, Inc.
Attention: Dara Wambach, M.A.
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Viread (tenofovir disoproxil fumarate).

We also refer to the telecon between representatives of your firm and the FDA on July 30, 2009. The purpose of this meeting was to discuss the filing of a pediatric NDA for Viread Oral Powder for the treatment of HIV-1 infected patients 2 to 18 years of age. This NDA also is being submitted to fulfill terms of the pediatric Written Request for Viread (amended January 29, 2008) and PREA postmarketing commitments.

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

If you have any questions, call Carrie Ceresa, Pharm D., MPH, Regulatory Project Manager at (301) 796-4108.

Sincerely,

{See appended electronic signature page}

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

Enclosure



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: July 30, 2009, 1:00 pm – 2:30 pm

Application Number: IND 52,849
Product Name: Viread (tenofovir disoproxil fumarate)
Indication: HIV-1 infected patients ages 2-18
Sponsor/Applicant Name: Gilead Sciences, Inc.

Meeting Chair: Linda Lewis, M.D., Medical Team Leader
Meeting Recorder: Carrie Ceresa, Pharm D., MPH, Regulatory Project Manager

FDA ATTENDEES

Debra Birnkrant, M.D.	Director
Jeff Murray, M.D.	Deputy Director
Vicky Tyson	Chief Project Management Staff
Linda Lewis, M.D.	Medical Team Leader
Mary Singer, M.D., Ph.D.	Clinical Reviewer
Narayana Battula, Ph.D.	Clinical Virology Reviewer
Greg Soon, Ph.D.	Biometrics Team Leader
Susan Zhou, Ph.D.	Biometrics Reviewer
Sarah Robertson, Pharm D.	Clinical Pharmacology Team Leader
Shirley Lu, Ph.D.	Clinical Pharmacology Reviewer
Justina Molzon, M.S. Pharm., J.D.	Associate Director for International Programs
Christine Malati, Pharm D.	Clinical Pharmacology Fellow
Carrie Ceresa, Pharm D., MPH	Regulatory Project Manager

SPONSOR ATTENDEES

Shan-Shan Chen, MPH., Sr.	Director, Biometrics
Andrew Cheng, M.D., Ph.D.	SVP Development Operations
Steven Chuck, M.D.	Sr. Director, Clinical Research
Pamela Danagher, M.Sc.	Director, Regulatory Affairs
Brian Kearney, PharmD.	Sr. Director, Clinical Research (Clinical Pharmacology)
Michael Miller, Ph.D.	Sr. Director, Virology
David Pizzuti, MD	VP Regulatory Affairs
Kirsten White, Ph.D.	Sr. Scientist I, Biology
Dara Wambach, M.A.	Sr. Manager, Regulatory Affairs
Michael Wulfsohn, M.D., Ph.D.	VP Biometrics

1.0 BACKGROUND

The purpose of this Pre-NDA meeting was to discuss the results from the pediatric clinical studies (Study GS-US-104-321 in adolescents and Study GS-US-104-0352 in patients ages 2 to 12) that will be submitted to support the treatment of HIV-1 infection in children 2-18 years of age with Viread tablets and an oral powder. In addition, this meeting was held to discuss the requirements of the Pediatric Written Request and PREA postmarketing commitments for Viread.

2.0 DISCUSSION

Question 1: Does the Agency have any comment on Gilead's proposed content and format of the NDA, and its plans to fulfill the requirements of the Pediatric Written Request for Viread, in order to secure Pediatric Exclusivity?

It appears that the proposed submission may meet the requirements of the Written Request (WR), however the current WR asks for studies that identify an appropriate dose for all age groups. In the 2 to 12 year age group, the selected dose of 8 mg/kg administered in Study 0352 provided lower tenofovir exposure than was observed in the adult clinical trials. No other dose was evaluated in this age group with the proposed powder formulation. We are concerned the failure to achieve the primary endpoint of Study 0352 was partially due to suboptimal exposure. The submission will be reviewed by both DAVP and the Pediatric Exclusivity Board to determine if it meets the conditions of the WR.

Please provide additional detail on which studies you propose to include in the ISS and ISE and how the datasets for the integrated summaries will be constructed. Please confirm that datasets for each study as well as integrated datasets will be provided.

Discussion

Gilead stated that they understand DAVP's concerns regarding the 8 mg/kg dose administered in Study 0352, but believe that this is the appropriate dose. Gilead evaluated patients with the lowest exposures in the PK substudy and found no relationship between low exposure and treatment outcome. The DAVP asked Gilead how many treatment failures were included in the PK substudy, and whether a more formal exposure-response analysis might be conducted using the PK substudy population. Gilead responded that they have pharmacokinetic data on only three of the subjects who were scored as failures.

Gilead stated that previous studies conducted with lower doses of approximately 5 and 7 mg/kg using the 75 mg tablet supports their dose selection of 8 mg/kg. The DAVP asked Gilead if the 75 mg tablet is composed of the same blend as the 300 mg tablet. Gilead responded that bioequivalence of the 75 and 300 mg tablets has been established in a previously conducted BE study. Gilead will submit the bioequivalence study in the oral powder NDA.

Question 2: Pending regulatory review of safety and PK data, does the Agency agree that Studies GS-US-104-0321 and GS-US-104-0352 would support an indication for use of Viread in the pediatric population (2 – < 18 years of age) despite the lack of conclusive demonstration of efficacy?

Whether or not these two studies will support an indication for Viread in patients 2 to < 18 years of age is a review issue. The failure of both studies to achieve the primary efficacy endpoint is disappointing. A request for approval based on extrapolation from adult efficacy data is an acceptable strategy but must be adequately supported with appropriate pediatric data. Careful review of all available safety data and bridging pharmacokinetic data will be conducted to support this approach. Descriptions of patient subsets in which activity can be shown as well as those in which activity must be extrapolated will need to be displayed in the label if approval is granted.

In this case, Study 0321 appears to provide adequate PK data to bridge to the dose of tenofovir found to be safe and effective in adult trials. A reasonable explanation for the study's failure to meet its primary objective is identified in the high levels of baseline reduced susceptibility to tenofovir in the heavily experienced study population. In the adolescent age group, we believe that extrapolation from the adult efficacy trials may be possible.

As mentioned above, in Study 0352, the study failed to meet the primary efficacy endpoint and also failed to achieve the target tenofovir exposure. Although the documented exposure in patients 2 to 12 years of age was not dramatically less than in the successful adult trials, this study provides neither adequate efficacy data by itself nor adequate bridging PK data to be certain that the appropriate dose has been selected for this age group.

Discussion: Gilead explained that there were other reasons why Study 0352 did not reach the primary endpoint other than inadequate exposure. Gilead stated that the failure to meet the primary endpoint was likely the result of early withdrawals and transient increases in HIV-RNA at Week 48 in a few subjects. The DAVP explained that the preliminary meeting responses were based on the summary data they had received. Gilead referred to Table 23 in the briefing package and stated that eight subjects were considered failures but three of these subjects went on to re-suppress below 50 copies/mL and there were two discontinuations. The DAVP asked Gilead if there is additional adult exposure-response data available that would support the level of exposure observed in Study 0352. The DAVP will look at the data very carefully and asked Gilead about the status of the 96 week data. The 96 week data will be available on about 76 subjects in December of 2009. **Gilead will provide the DAVP with the available 96 week data, as well as the date it will be submitted for review.**

Question 3: Does the Agency have any comments or are there additional considerations for discussion based upon this plan?

One alternative is to amend the deadline for the final submission of pediatric study data under the WR and use the extension to evaluate a higher dose of tenofovir DF in the patients remaining in Study 0352. Study 0321 could be submitted as an efficacy supplement to NDA 21-356 allowing review of the data for adolescent patients and possible approval in that age group. Study 0352 could be submitted to the new Oral Powder NDA at a later time with exclusivity determination performed at that time.

Discussion: Gilead will submit a request to extend the deadline for the pediatric Written Request for ages 2-12 years and will submit the NDA for use of Viread Oral Powder in this age group when the 96 week data is available for review. Gilead will submit an efficacy supplement to NDA 21-356 for use of Viread tablets in pediatric patients ages 12-18.

*The DAVP informed Gilead that a determination of exclusivity will be made by the DAVP and the Pediatric Exclusivity Board; and that determination is made prior to the review of the NDA submitted to support an indication. The DAVP informed Gilead that the request for exclusivity should be submitted when the NDA is submitted and the Board may have concerns with the dose administered in Study 0352. The DAVP has not seen the exposure-response data and raised the possibility of conducting a study with higher doses in subjects 2-12 years of age. Gilead would like to ensure that they meet the WR and asked about procedures to request an extension of the WR. The DAVP advised Gilead to request an extension of the WR to allow for collection and analysis of the 96 week data; however the determination of exclusivity will be a review issue. **Gilead will submit a request to amend the WR in two to three weeks.***

Question 4: Does the Agency agree with the plans for content and submission timing for the NDA Safety Update?

If you proceed with submission, the proposal for submission of the safety update is acceptable.

Additional Comments:

Gilead asked for clarification on Clinical Microbiology items 5 and 6 of the preliminary comments.

5. Please add columns to the virology datasets for the GSS score(s).

Discussion: Gilead asked if the Division is asking for the GSS score for the total regimen or individual drugs. The Division replied that GSS scores for the total regimen and individual drugs be provided according to both ANRS and Stanford algorithms.

6. Please provide detailed descriptions of the GSS algorithms(s) used and describe how each subject's genotype fits their GSS score(s).

Discussion: Gilead asked if the Division is requesting a narrative or the data or both a narrative and data. The DAVP responded that we would like both the narrative and data on a subset of patients.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.

4.0 ACTION ITEMS

- Gilead will submit a response to the clinical pharmacology information requested in the preliminary meeting comments in the next two weeks.
- Gilead will evaluate available exposure-response data from adults and submit a timeline for submission of the data in the next two weeks.
- Gilead plans to submit a request to extend the pediatric Written Request.
- Gilead will submit an efficacy supplement to Viread tablet NDA 21-356 for pediatric patients 12 to 18 years of age. This efficacy supplement will not include a request for exclusivity.
- Gilead will submit an NDA for Viread Oral Powder once the 96 week data is ready for submission and review and will include the clinical virology data requested in the preliminary meeting comments.

5.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 52849	GI 1		PMPA
IND 52849	GI 1		PMPA

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

/s/

DEBRA B BIRNKRANT
08/19/2009