

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206510Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206510

SUPPL # S-000

HFD # 530

Trade Name Dutrebis

Generic Name lamivudine and raltegravir

Applicant Name Merck

Approval Date, If Known February 6, 2015

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)(2)

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

YES NO

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

The basis of approval are BA/BE studies comparing the individual products to the fixed dose product. Study P253 entitled, "MK0518B Bioequivalence Study", compared lamivudine/RAL fixed dose combination to lamivudine and raltegravir individual products.

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 22145	Isentress (raltegravir)
NDA# 203045	Isentress (raltegravir)
NDA# 205786	Isentress (raltegravir)
NDA# 21004	Epivir-HBV (lamivudine) oral solution
NDA 20596	Epivir (lamivudine) oral solution
NDA 20564	Epivir (lamivudine) tablets
NDA 21003	Epivir-HBV (lamivudine) tablets
NDA 20857	Combivir (lamivudine/zidovudine) tablet
NDA 21652	Epzicom (abacavir sulfate and lamivudine
NDA 20551	Triumeq (abavavir, dolutegravir sodium, lamivudine
NDA 21205	Trizivir (abacavir sulfate, lamivudine, zidovudine

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:

Both products are approved and the only data necessary for approval is the BE study.

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation

and the NDA in which each was relied upon:

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

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

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

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: Mammah Sia Borbor, M.S., M.B.A.
Title: Regulatory Project Manager
Date: January 28, 2015

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

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MAMMAH S BORBOR
02/06/2015

JEFFREY S MURRAY
02/06/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 206510 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Dutrebis Established/Proper Name: lamivudine/raltegravir Dosage Form: tablets		Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):
RPM: Mammah Sia Borbor, M.S., M.B.A.		Division: Antiviral Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: December 23, 2014</p> <p><i>Note: 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.</i></p>	
Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is _____ 	<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	
❖ 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 _____	<input type="checkbox"/> Received	
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ 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.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
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 (including approval letter with final labeling)	Action(s) and date(s) February 6, 2015
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> • Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input 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) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (indicate date(s)) • Review(s) (indicate date(s)) 	September 12, 2014 September 8, 2014
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> PLR Format Review July, 8, 2014 None DMEPA: <input checked="" type="checkbox"/> August 18, 2014 None DMPP/PLT (DRISK): X January 22, 2015 <input type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> January 22, 2015 None SEALD: <input type="checkbox"/> None X CSS: <input type="checkbox"/> None X Other: <input type="checkbox"/> None X
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	June 9, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	January 5, 2015 <input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ 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

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<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>January 7, 2015</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	February 2, 2015, January 28, 2015, January 27, 2015, January 26, 2015, January 11, 2015, January 5, 2015, November 17, 2014, September 5, 2014, August 6, 2014, July 15, 2014, May 29, 2014, May 28, 2014, May 23, 2014, June 20, 2014 and April 21, 2014
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	None
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input type="checkbox"/> N/A or no mtg <input checked="" type="checkbox"/> <i>Pre NDA Preliminary Comments April 18, 2012</i> No mtg <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> N/A <input type="checkbox"/> N/A N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None X
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None X
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> January 18, 2015 None
PMR/PMC Development Templates	<input type="checkbox"/> None
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review December 30, 2014 <input checked="" type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	February 2, 2015, Clinical Pharmacology Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<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"/> December 17, 2014 None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI 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"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 11, 2014
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None February 2, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	January 27, 2015, January 22, 2015 and December 19, 2014
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None January 8, 2015
❖ 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
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality	<input type="checkbox"/> None
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Product Quality Review February 5, 2015 Biopharmaceutics Review February 1, 2015
❖ Microbiology Reviews	<input type="checkbox"/> Not needed August 18, 2014
<input checked="" 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>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	January 2, 2015 taken from product quality review pg. 113
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
• Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: February 5, 2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ 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.

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input checked="" type="checkbox"/> Done



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510

Drug: Dutrebis lamivudine/raltegravir (150 mg/300 mg) FDC tablet

Date: February 2, 2015

To: Joanna Pols, Ph.D.

Sponsor: Merck Sharp & Dohme Corp.

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager

Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments in the attached label (PI) are being conveyed on behalf of the review team for your application.

The availability of this information is critical for DAVP's review regarding the proposed labeling. As a result we ask that you provide a response to the **Division by COB Tuesday, February 3, 2015.**

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
02/02/2015

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206510

Submission Date(s): 8 April 2014

Applicant: Merck Sharp & Dohme Corp.

Product: Lamivudine/raltegravir

Reviewer: Leslie Chinn, Ph.D.

Date of Review: 2 February 2015

Covered Clinical Study (Name and/or Number): P253

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>3</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

None of the clinical investigators had disclosable financial interests or arrangements. Financial disclosures do not affect the approvability of this application.

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/s/

LESLIE W CHINN
02/02/2015

From: [Pols, Joanna](#)
To: [Borbor, Mammah](#)
Subject: RE: NDA 206510 updated PI (section 7.3)
Date: Wednesday, January 28, 2015 3:37:03 PM

Great. Thank you.
Joanna

From: Borbor, Mammah [<mailto:Mammah.Borbor@fda.hhs.gov>]
Sent: Wednesday, January 28, 2015 3:35 PM
To: Pols, Joanna
Subject: RE: NDA 206510 updated PI (section 7.3)
Importance: High

Hello Joanna,

Thanks kindly for contacting me. I have confirmed with our team that [REDACTED] (b) (4) can be deleted.

Thanks kindly,
Mammah

Mammah Sia Borbor, MS, MBA

Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6395
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.7731
Fax: 301.796.9883
Email: mammah.borbor@fda.hhs.gov

From: Pols, Joanna [<mailto:joanna.pols@merck.com>]
Sent: Wednesday, January 28, 2015 2:57 PM
To: Borbor, Mammah
Subject: RE: NDA 206510 updated PI (section 7.3)

Hello Mammah,

I am writing regarding one item that we would like to clarify.

In section 8.4 (Pediatric Use) of the USPI, there is an incomplete statement [REDACTED] (b) (4) inserted at the end of the paragraph within the *DUTREBIS* subsection. The text is not shown as tracked within the USPI we received. Please confirm whether there should be a cross-reference statement here or whether this text was inserted in error.

Thank you,

Joanna

From: Borbor, Mammah [<mailto:Mammah.Borbor@fda.hhs.gov>]
Sent: Tuesday, January 27, 2015 11:37 AM
To: Pols, Joanna
Subject: NDA 206510 updated PI (section 7.3)
Importance: High

Hello Joanna,

Per my previous email and voicemail message today attached please find a copy of an updated PI specifically section 7.3. Please use this version to make any updates. I apologize for the last minute changes. Please feel free to contact me if you have any additional questions or concerns.

As usual I have attached a copy of the label (PI & PPI) in word version for your convenience.

Thanks kindly,
Mammah

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/s/

MAMMAH S BORBOR
01/28/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510

Drug: lamivudine/raltegravir (150 mg/300 mg) FDC tablet

Date: January 27, 2015

To: Joanna Pols, Ph.D.

Sponsor: Merck Sharp & Dohme Corp.

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager

Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments below along with the attached label (PI & PPI) are being conveyed on behalf of the review team for your application.

Clinical

1. Please ensure the Warnings and Precautions are listed in decreasing order of clinical significance.

Product Quality

2. For the bottle label, we recommend replacing: (b) (4)

With: Each tablet contains 150 mg lamivudine and 325.8 mg raltegravir potassium, equivalent to 300 mg raltegravir.

Comparable changes should be made throughout the package insert/patient package insert where equivalency of raltegravir potassium to raltegravir free phenol is made:

3. In the patient package insert, reference to [REDACTED] (b) (4) should be revised to desiccant [REDACTED] (b) (4).

The availability of this information is critical for DAVP's review regarding the proposed labeling. As a result we ask that you provide a response to the **Division by Friday, January 30, 2015.**

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
01/27/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510
Drug: lamivudine/raltegravir (150 mg/300 mg) FDC tablet
Date: January 26, 2015
To: Joanna Pols, Ph.D.
Sponsor: Merck Sharp & Dohme Corp.
From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments below along with the attached label (PI & PPI) are being conveyed on behalf of the review team for your application.

Clinical

1. Please ensure the Warnings and Precautions are listed in decreasing order of clinical significance.

Product Quality

2. For the bottle label, we recommend replacing: (b) (4)

With: Each tablet contains 150 mg lamivudine and 325.8 mg raltegravir potassium, equivalent to 300 mg raltegravir.

Comparable changes should be made throughout the package insert/patient package insert where equivalency of raltegravir potassium to raltegravir free phenol is made:

3. In the patient package insert, reference to [REDACTED] (b) (4) should be revised to desiccant [REDACTED] (b) (4).

The availability of this information is critical for DAVP's review regarding the proposed labeling. As a result we ask that you provide a response to the **Division by Friday, January 30, 2015.**

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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MAMMAH S BORBOR
01/26/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510
Drug: lamivudine/raltegravir (150 mg/300 mg) FDC tablet
Date: January 09, 2015
To: Joanna Pols, Ph.D.
Sponsor: Merck Sharp & Dohme Corp.
From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments below along with the attached label are being conveyed on behalf of the review team for your application.

Product Quality

1. For the bottle label, we recommend replacing: (b) (4)
[Redacted]

With: Each tablet contains 150 mg lamivudine and 325.8 mg raltegravir potassium, equivalent to 300 mg raltegravir.

Comparable changes should be made throughout the package insert/patient package insert where equivalency of raltegravir potassium to raltegravir free phenol is made:

2. In the patient package insert, reference to (b) (4)
desiccant (b) (4) should be revised to

The availability of this information is critical for DAVP's review regarding the proposed labeling. As a result we ask that you provide a response to the Division by Friday, January 16, 2015.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
01/11/2015

From: [Borbor, Mammah](#)
To: [Pols, Joanna \(joanna.pols@merck.com\)](mailto:joanna.pols@merck.com)
Subject: NDA 206510 Agreed Pediatric Study Plan
Date: Monday, January 05, 2015 11:07:54 AM
Importance: High

Hello Joanna,

The Pediatric Study Plan was erroneously labeled in your original submission sent on 4/8/2014 as a PPSR. Please acknowledge and resubmit the document to the NDA as an Agreed Initial Pediatric Study Plan.

Thanks kindly,

Mammah

Mammah Sia Borbor, MS, MBA

Regulatory Project Manager

Division of Antiviral Products (DAVP)

FDA/CDER/OND/OAP

White Oak Complex, Bldg 22, Rm 6395

10903 New Hampshire Ave.

Silver Spring, MD 20993

Ph: 301.796.7731

Fax: 301.796.9883

Email: mammah.borbor@fda.hhs.gov

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/s/

MAMMAH S BORBOR
01/05/2015

From: [Borbor, Mammah](#)
To: [Pols, Joanna \(joanna.pols@merck.com\)](mailto:joanna.pols@merck.com)
Subject: NDA 206510
Date: Monday, January 05, 2015 10:07:44 AM
Attachments: [11-17-2014 Comments & Label to Sponsor.pdf](#)
Importance: High

Hello Joanna,

On November 17, 2014 we sent labeling comments along with the label to Merck. We received a submission back from Merck on December 9, 2014. In reviewing the submission, we did not see a response to our comment LC18 in the label we sent to you on 11/17. Please send your response back to me via email (ASAP-preferably by the COB today as we have a meeting scheduled for tomorrow) justifying the use of Isentress Phase 3 data for the omeprazole recommendation. You can send the response formally to the NDA by the end of the week.

P.S. I have attached a copy of the label sent on November 17, 2014 for your convenience.

Thanks kindly,

Mammah

Mammah Sia Borbor, MS, MBA

Regulatory Project Manager

Division of Antiviral Products (DAVP)

FDA/CDER/OND/OAP

White Oak Complex, Bldg 22, Rm 6395

10903 New Hampshire Ave.

Silver Spring, MD 20993

Ph: 301.796.7731

Fax: 301.796.9883

Email: mammah.borbor@fda.hhs.gov

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/s/

MAMMAH S BORBOR
01/05/2015

From: Bhandari, Navi
To: "joanna.pols@merck.com"
Cc: Cuff, Althea
Bcc: Eradiri, Okpo
Subject: NDA 206510: Biopharmaceutics Information Request
Date: Monday, January 05, 2015 7:32:00 AM
Importance: High

Hello Joanna,

My review team has asked that you provide a response to the following comment by January 12, 2015:

“Submit the individual vessel dissolution data (at release) for the clinical batch of Lamivudine/Raltegravir FDC Tablets (WL00049346) used in the pivotal bioequivalence study, P253. Note that these data are needed for assessment of adequacy of your proposed dissolution acceptance criterion for both active components. In addition, while the report for Study P253 lists only WL00049346 as the test product batch, your summary in section 2.7.1 of the Application indicates that Batch WL00047480 was also used in the study. If this second lot was used in Study P253, provide the dissolution profile data at release for it as well. Based on the available data, the dissolution acceptance criterion you propose ^{(b) (4)} does not seem to be adequate. Revise the proposed dissolution acceptance criteria based on the data from the batches used in the pivotal bioequivalence study.

In order to aid review of the data sets you will be providing, please include the following:

- a) Composite plot of the individual vessel dissolution profile data at release and at time zero stability time point for both active components in the clinical batch(es) used in Study P253 as well as the registration batches.**
- b) Composite plots of individual vessel percent dissolved values at 30 min and 45 min; the plots should include data at release and at all stability time points. Please include the dissolution data generated in the stability program for the clinical and primary stability batches.**
- c) A tabular summary of the dissolution data on clinical and registration batches including (for each time point) the number of batches, overall mean, range of means, range of individual vessel values, SD and overall %CV.”**

Please confirm receipt of this correspondence.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510

Drug: lamivudine/raltegravir (150 mg/300 mg) FDC tablet

Date: November 17, 2014

To: Joanna Pols, Ph.D.

Sponsor: Merck Sharp & Dohme Corp.

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager

Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments are being conveyed on behalf of the review team for your application.

Clinical

1. Please find the attached label with the review team's suggested revisions and comments.
2. The review team has not yet edited the PPI and is requesting the Sponsor please make edits based on the PI revisions.

Product Quality

3. Please revise the package insert (e.g., the Dosage Forms and Strengths section and the Description section) and container label to include statements regarding raltegravir salt equivalence.
4. Please revise the storage statements in the package insert and container label to include, "See USP Controlled Room Temperature."

5. Please revise Section 11, Description, of the package insert to include the pharmacological or therapeutic class of each active ingredient.
6. Please note that the SPL Data Elements should be revised to indicate that, although active moiety ingredient name and the basis of strength is raltegravir, the active ingredient is raltegravir potassium (see Isentress SPL).
7. Please revise the statement, [REDACTED] (b) (4) [REDACTED] to “Raltegravir potassium is a human immunodeficiency virus integrase strand transfer inhibitor.”

The availability of this information is critical for DAVP’s review regarding the proposed labeling. As a result we ask that you provide a response to the Division by Friday, November 28, 2014.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
11/17/2014



NDA 206510

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corporation
P.O. Box 2000, 126 East Lincoln Avenue
RY33-212
Rahway, NJ 07065

ATTENTION: Joanna Pols, Ph.D.
Director, Global Regulatory Affairs

Dear Dr. Pols:

Please refer to your New Drug Application (NDA) dated and received April 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamivudine/Raltegravir Tablets, 150 mg/300 mg.

We also refer to your correspondence dated and received July 3, 2014, requesting review of your proposed proprietary name, Dutrebis. We have completed our review of the proposed proprietary name Dutrebis, and have concluded that this name is acceptable.

If **any** of the proposed product characteristics as stated in your July 3, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager Mammah Borbor, at (301) 796-7731.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

AZEEM D CHAUDHRY
09/12/2014

KELLIE A TAYLOR
09/12/2014

From: [MacDonald, Laurie](#)
To: [Borbor, Mammah](#)
Cc: [Pols, Joanna](#)
Subject: RE: MK-0518B (NDA 206-510) Paragraph IV certification
Date: Monday, August 25, 2014 12:20:04 PM

Hi Mammah,

As of today, August 25, 2014, Merck has not been notified by [REDACTED] (b) (4)

Best regards,
Laurie

Laurie J. MacDonald, MD
Executive Director, Global Regulatory Affairs
Therapeutic Area Lead - Infectious Diseases
Merck & Co., Inc.
Phone: 267-305-5540

From: Borbor, Mammah [mailto:Mammah.Borbor@fda.hhs.gov]
Sent: Monday, August 25, 2014 9:55 AM
To: MacDonald, Laurie
Cc: Pols, Joanna
Subject: RE: MK-0518B (NDA 206-510) Paragraph IV certification
Importance: High

Hello Joanna,

I am just following up regarding the Paragraph IV certification sent to [REDACTED] (b) (4). I have noted that [REDACTED] (b) (4) last day to respond was Saturday, August 23, 2014. Please let me know if [REDACTED] (b) (4) has responded.

Thanks kindly,
Mammah

Mammah Sia Borbor, MS, MBA

Regulatory Project Manager
Division of Antiviral Products (DAVP)
FDA/CDER/OND/OAP
White Oak Complex, Bldg 22, Rm 6395
10903 New Hampshire Ave.
Silver Spring, MD 20993
Ph: 301.796.7731
Fax: 301.796.9883
Email: mammah.borbor@fda.hhs.gov

From: Pols, Joanna [mailto:joanna.pols@merck.com]
Sent: Friday, August 15, 2014 4:24 PM
To: Borbor, Mammah; Cuff, Althea; Bhandari, Navdeep

Cc: Abeygunawardana, Chitrananda; MacDonald, Laurie; Gutsch, David; Pols, Joanna
Subject: MK-0518B (NDA 206-510) Vacation Back-up Information

Dear All:

I wanted to inform you that I will be on vacation August 18-September 2.

Please feel free to contact the following individuals during my absence:

Aug 18-Aug 22 Abey Chitrananda
Aug 25-26 Laurie MacDonald
Aug 29-Sep 2 David Gutsch

I have asked Abey to provide a response early next week regarding the request for information (received on August 13) on the location of records from the Oss site.

In addition, the response to the CMC request for information (received on August 6) is being planned for August 29, 2014.

Kind regards,
Joanna

Joanna Pols, Ph.D.

Director, Worldwide Regulatory Liaison

Global Regulatory Affairs

T: +732-594-7361
joanna.pols@merck.com

Merck Research Laboratories

126 East Lincoln Ave.

RY33-212

Rahway, NJ 07065

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/s/

MAMMAH S BORBOR
09/05/2014

From: Bhandari, Navdeep
To: ["joanna.pols@merck.com"](mailto:joanna.pols@merck.com)
Subject: NDA 206510 Information Request
Date: Wednesday, August 06, 2014 2:23:00 PM
Importance: High

Hello Joanna,

My review team has asked that you provide a response to the following comment by **August 31, 2014**:

1. The dissolution experiments you conducted to select the suitable medium (Fig 1 in Module 3, section 3.2.P.5.6) do not specify the paddle speed(s) used. Provide the paddle rotation speed(s) and the number of units tested in each experimental run; in addition, provide the complete data (individual and mean values in tabular and graphical forms) over a range of rotation speeds.
2. The data and information on the discriminating capability of your proposed dissolution method are incomplete. For each parameter investigated [REDACTED] (b) (4), identify the numerical value or range used for the target formulation; thereafter, change the parameters [REDACTED] (b) (4) of the target to make variant formulations. The resulting dissolution profiles (n=12) of the variant formulations should be compared to the target profile using the f2 Similarity test or some other suitable statistical test. Please provide complete data on the investigations. The results of these experiments should be reported in graphical and tabular forms.

Please confirm receipt of this correspondence.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
08/06/2014

Cuff, Althea

From: Cuff, Althea
Sent: Tuesday, July 15, 2014 11:37 AM
To: 'joanna.pols@merck.com'
Cc: Borbor, Mammah
Subject: NDA 206510 - Information Request

A product quality microbiology review of NDA 206-510 is in progress and the following information is requested by August 4, 2014:

We refer to your 03 July 2014, response to question 6 from the filing communication regarding the holding time (b)(4). The data presented in Table 6 do not allow for an evaluation of the potential for microbial proliferation (b)(4) during the proposed (b)(4) hold time.

1. Provide the time interval between the samples collected (b)(4) for batches 1015680, 1015690, and 1015700.
2. If applicable, describe any (b)(4) steps involved in the (b)(4) preparation.

With the proposed absence of any routine microbial enumeration release studies the upstream controls (b)(4) are critical to control the final bioburden in the proposed drug product. If the sample interval for batch 1015680 does not approach the proposed (b)(4) interval, then justify the proposed (b)(4) hold time. Historical data from similar products may be applicable and could be used to support the proposed (b)(4) hold time.

Thanks

*Althea Cuff, MS
Regulatory Health Project Manager
Food & Drug Administration, CDER
Office of New Drugs Quality Assessment II
301-796-4061*

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/s/

ALTHEA CUFF
07/15/2014



NDA 206510

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.
Attention: Joanna Pols, Ph.D.
Director, Global Regulatory Affairs
PO Box 2000
126 East Lincoln Avenue, RY33-212
Rahway, NJ 07065

Dear Dr. Pols:

Please refer to your New Drug Application (NDA) dated April 8, 2014, received April 8, 2014 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for lamivudine and raltegravir tablet, 150 mg\300 mg.

We also refer to your amendment dated April 24, 2014.

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 **Standard**. Therefore, the user fee goal date is February 8, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by January 11, 2015.

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

We request that you submit the following information by July 3, 2014:

CLINICAL PHARMACOLOGY

1. Please submit the following information to assist in the review of your modeling and simulation report “03tsw9” and specify where in the provided submission the materials may be located:
 - NONMEM codes for simulation of adult and pediatric PK profiles
 - Model-predicted exposure data (AUC, C_{max} , and C_{12hr}) for adults and pediatric subjects and codes (such as Splus, SAS, or R, etc.) used for calculating these parameters
 - Your data and codes (NONMEM, SAS, Splus, R, etc.) for PK/PD analysis (viral dynamic model)

PRODUCT QUALITY CHEMISTRY

2. Please submit a copy of the commercial drug product master production record.

PRODUCT QUALITY BIOPHARMACEUTICS

3. Provide the complete individual vessel dissolution profile data and descriptive statistics for Lamivudine and Raltegravir. Provide these data in excel format. We acknowledge that you have provided the range and mean percent dissolved values for both drug components in sections 3.2.P.5.4 and 3.2.P.8.3; however, please also provide measures of variability at each sampling time point, i.e., %CV, SD.

PRODUCT QUALITY MICROBIOLOGY

4. We refer to Module 3.2.P.8.1.2.5. Justify the inclusion of USP<61> but not USP<62> tests for the formal stability batches WL00047478, WL00047479, and WL00047480. USP<1111> recommends the absence of *Escherichia coli* for solid oral dosage forms and any deviations from these recommendations should be justified.
5. Confirm that the USP microbial enumeration studies were verified to be suitable for use according to the methods described in USP<61> and <62>.
6. Provide the maximum hold time, or a bioburden specification, (b) (4). Any extended hold times should be supported by data that demonstrate low levels of contaminating microorganisms will not proliferate to unsafe levels.
7. You propose waiving microbial limits release testing for your drug product. This will be evaluated during the review process and after receipt of the information requested here. However, you should minimally perform microbiological testing at the initial stability time point for the annual stability batches. Provide an updated stability schedule to reflect this testing. Include the proposed limits for USP<61> and <62> test methods.

VIROLOGY

8. Provide a pooled dataset as a SAS transport file including genotypic resistance data summarized in Appendix Table 1 of the study report PD001.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

FULL PRESCRIBING INFORMATION: CONTENTS*

1. The same heading for the BOXED WARNING that appears in the HIGHLIGHTS and the FULL PRESCRIBING INFORMATION must also appear at the beginning of the table of contents. The heading is slightly different.

FULL PRESCRIBING INFORMATION (FPI): ADVERSE REACTIONS section:

2. The following statement should be removed from section 6, and placed at the beginning of sections 6.1, (b) (4): “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”
3. The following statement should precede the presentation of adverse reactions that have been identified during post approval drug use: (b) (4)

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 11, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

We note that you have submitted pediatric studies with this application for pediatric patients 6 to 16 years of age weighing at least 30 kg. 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 Mammah Sia Borbor, M.S., M.B.A., Regulatory Project Manager, at (301) 796-7731 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

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/s/

MAMMAH S BORBOR
06/20/2014

DEBRA B BIRNKRANT
06/20/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510

Drug: lamivudine/raltegravir (150 mg/300 mg) FDC tablet

Date: May 29, 2014

To: Joanna Pols, Ph.D.

Sponsor: Merck Sharp & Dohme Corp.

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager

Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments are being conveyed on behalf of the review team for your application.

1. We are able to locate the bioanalytical reports for lamivudine in Module 5.3.1.2 under Appendices 16.1.11 for P253, P258, and P260. However, we are unable to locate the bioanalytical reports for raltegravir, the other component of the fixed-dose combination tablet under review in NDA 206510. Please submit the raltegravir bioanalytical reports or an updated location within the application (including page number within a document, if necessary) as requested yesterday.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
05/29/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510

Drug: lamivudine/raltegravir (150 mg/300 mg) FDC tablet

Date: May 28, 2014

To: Joanna Pols, Ph.D.

Sponsor: Merck Sharp & Dohme Corp.

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager

Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments are being conveyed on behalf of the review team for your application.

1. We were unable to locate the bioanalytical reports for raltegravir for the three BA/BE studies. Please submit the raltegravir bioanalytical report for study P253 by Friday, May 30, 2014 COB and the raltegravir bioanalytical reports for studies P258 and P260 by Friday, June 13, 2014 COB. If these reports have already been submitted to the NDA, please provide the location within the submission.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
05/28/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

NDA: 206510

Drug: lamivudine/raltegravir (150 mg/300 mg) FDC tablet

Date: May 23, 2014

To: Joanna Pols, Ph.D.

Sponsor: Merck Sharp & Dohme Corp.

From: Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager

Subject: NDA 206510

Please reference your submission dated April 8, 2014. The following comments are being conveyed on behalf of the review team for your application.

1. Please submit the bioanalytical report for study P253 by **Friday, May 30, 2014 COB**. If this report has already been submitted to the NDA, please provide the location within the submission.
2. Please submit the bioanalytical reports for studies P258, P260, and P254 by **Friday, June 13, 2014 COB**. If these reports have already been submitted to the NDA, please provide the location within the submission.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE**. Please feel free to contact me at 301-796-7731 if you have any questions regarding the contents of this transmission.

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
05/23/2014



NDA 206510

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Joanna Pols, Ph.D.
Director, Global Regulatory Affairs
PO Box 2000
126 East Lincoln Avenue, RY33-212
Rahway, NJ 07065

Dear Dr. Pols:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: lamivudine/raltegravir tablet, 150mg, 300mg

Date of Application: April 8, 2014

Date of Receipt: April 8, 2014

Our Reference Number: NDA 206510

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 June 7, 2014, 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>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Mammah Sia Borbor, Regulatory Project Manager, at (301) 796-7731 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
04/21/2014

MK-0518B LAMIVUDINE/RALTEGRAVIR FDC

1.6.3 Correspondence Regarding Meetings

A Pre-NDA Meeting (teleconference) was held 20-Nov-2013, and the official minutes were received on 02-Dec-2013.



IND 113,176

MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Joanna Pols, PhD
Director, Global Regulatory Affairs
PO Box 2000 126 East Lincoln Avenue, RY33-212
Rahway, NJ 07065

Dear Dr. Pols:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0518B (lamivudine/raltegravir) fixed-dosed combination (FDC).

We also refer to the telecon between representatives of your firm and the FDA on November 20, 2013. The purpose of the meeting was to discuss the content and format of your planned NDA for MK-0518B FDC.

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

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: November 20, 2013, 11:00 AM to 12:30 PM
Meeting Location: Teleconference

Application Number: IND 113,176
Product Name: MK-0518B (lamivudine/raltegravir) fixed-dosed combination tablet
Indication: Treatment of HIV-1 infection
Sponsor/Applicant Name: Merck Sharp & Dohme Corp.

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Sohail Mosaddegh, PharmD

FDA ATTENDEES

1. Debra Birnkrant, MD, Director
2. Karen Winestock, Chief, Project Management Staff, DAVP
3. Kendall Marcus, MD, Deputy Director of Safety
4. Kim Struble, PharmD, Medical Team Lead
5. Leslie Chinn, PhD, Clinical Pharmacology Reviewer
6. Mario Sampson, PhD, Pharmacologist
7. Nina Mani, PhD, MPH
8. Okpo Eradiri, PhD, Biopharmaceutics Reviewer
9. Sarita Boyd, PharmD, Clinical Reviewer
10. Sohail Mosaddegh, PharmD, Regulatory Project Manager
11. Stephen Miller, PhD, CMC-Lead, ONDQA
12. Sung Rhee, PhD, Virology Reviewer
13. Vikram Arya, PhD, Clinical Pharmacology Reviewer

EASTERN RESEARCH GROUP ATTENDEES

14. Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

15. Nicholas Kartsonis, MD, Executive Director, Clinical Research
16. Randi Leavitt, MD, PhD, Distinguished Scientist, Clinical Research
17. Peter Sklar, MD, MPH, Senior Principal Scientist, Clinical Research
18. Sandy Rawlins, Associate Principal Scientist, Clinical Research
19. Paul Fackler, PhD, Associate Vice President, Biopharmaceutics

Meeting Minutes
Meeting Type B

20. Valerie Schulz, MS, Associate Principal Scientist, Early Stage Development
21. Larissa Wenning, PhD, Senior Principal Scientist, Modeling & Simulation
22. Venkatesh Pilla Reddy, PhD, Associate Principal Scientist, Pharmacokinetics, Pharmacodynamics and Drug Metabolism
23. Anthony Rodgers, PhD, Senior Principal Scientist, Biostatistics
24. Dalya Guris, MD, MPH, Executive Director, Project Leadership
25. P. Markus Dey, PhD, Senior Principal Scientist, Preclinical Development
26. Jeffrey Ding, PhD, Director, Regulatory Affairs, Pharmaceutical CMC
27. Ekopimo Ibia, MD, MPH, Director, Regulatory Affairs, US Regulatory Policy
28. Joanna Pols, PhD, Director, Global Regulatory Affairs
29. David Gutsch, MD, Executive Director, Global Regulatory Affairs

Meeting Minutes
Meeting Type B

BACKGROUND

MK-0518B is a fixed-dose combination tablet of reformulated raltegravir and lamivudine to be administered twice daily, and is being developed for an indication in combination with other antiretroviral agents for the treatment of HIV-1. The sponsor plans to submit an NDA for MK-0518B as a 505(b)(2) application in early 2014. No Phase 2/3 clinical studies were conducted with MK-0518B in HIV-infected patients. The sponsor proposes to refer to a Phase 2 dose-ranging study (P004) previously submitted to the NDA 22-145. The purpose of this meeting is to discuss the content and format of the planned NDA for MK-0518B.

DISCUSSION

The sponsor's responses to DAVP's November 15, 2013 preliminary comments are in *italics*, followed by sponsor's responses submitted on November 19, 2013 in **bold**. Meeting discussion, if any, follows in regular font. The meeting focused on FDA's additional comment 4 and 5 of the Preliminary Comments document.

Additional Comments from DAVP's November 15, 2013 preliminary comments:

CLINICAL PHARMACOLOGY:

4) *Please ensure that previously characterized formulation-dependent interactions (e.g. antacids containing polyvalent cations) are evaluated using the to-be-marketed formulation.*

Merck response: Drug-drug interactions (DDIs) that affect raltegravir PK can be roughly divided into those that affect raltegravir clearance (e.g., rifampin), and those that affect absorption (e.g., omeprazole, antacids). The DDIs that affect clearance would not be expected to be impacted by the differences in formulation or raltegravir PK profile between MK-0518B and the currently marketed ISENTRESS® formulation. DDIs that affect absorption may be affected by the differences in bioavailability and/or PK profile between MK-0518B and ISENTRESS® and can be further divided into 2 categories: 1) those that increase raltegravir PK due to increased absorption, and 2) those that decrease raltegravir PK due to interactions with metal cations. For DDIs in the first category (e.g., omeprazole, or other agents that may increase gastric pH and thus increase solubility of raltegravir), the magnitude of increase is bounded by increases in bioavailability, which cannot exceed 100%. Since the MK-0518B formulation has a higher bioavailability relative to the ISENTRESS® formulation, increases in raltegravir PK by this mechanism will be similar to or less than those observed with the ISENTRESS® formulation, and are thus not a concern for safety or efficacy of MK-0518B (for example, if the absolute bioavailability of ISENTRESS® is assumed to be ~30%, then an increase in bioavailability to 100% would result in an approximately 3-fold increase in AUC. The absolute bioavailability of the raltegravir component of MK-0518B would then be ~40%, and an increase in bioavailability to 100% would represent only a 2.5-fold increase in AUC). Therefore, Merck proposes that the labeling for MK-0518B will be consistent with

Meeting Minutes
Meeting Type B

the ISENTRESS® prescribing information, which recommends no dose adjustment for proton pump inhibitors and H2-blockers (e.g., omeprazole, famotidine).

For interactions related to metal cations (e.g., antacids), the interaction is likely to be a function of both gastric pH and the active ingredient (raltegravir), rather than formulation composition. The differences in PK profile between MK-0518B and ISENTRESS® are small enough that it is unlikely that a larger interaction will be observed between metal cations and MK-0518B, but it is possible that a similar interaction would be observed. Therefore, Merck proposes that the labeling for MK-0518B will state

(b) (4)

(b) (4)

consistent with the ISENTRESS® prescribing information.

Discussion: FDA stated that if, during the NDA review process, the Agency determines that additional data are needed regarding the clinical pharmacology issues described above, these issues will be addressed via discussions during the review process and the necessary data can be provided post approval.

Post meeting comment: FDA agrees that drug-drug interactions in which raltegravir clearance is altered do not need to be assessed with MK-0518B. However, interactions affecting absorption can be affected by formulation and should therefore be addressed. Please comment on the following points when you submit your NDA so that the potential for and extent of these interactions can be assessed. These points can be discussed further following NDA submission and the Division's review of the relevant data.

- The absolute bioavailability of ISENTRESS may be 30%, but it may be lower; therefore, the increase in bioavailability may be greater than anticipated (while remaining less than or equal to 100%) in the presence of drugs that increase raltegravir absorption (e.g. omeprazole).
- Please address the differences in raltegravir formulation in IND 69928 and IND 113176 that require that the interaction between raltegravir and omeprazole be evaluated under the first IND but not under the second.
- Interactions in which raltegravir absorption is affected by metal cation chelation may be influenced by formulation as the extent and rate of dissolution may affect the degree of chelation at specific timepoints. In vitro data (e.g. dissolution data) may be useful to support your statements that the PK profiles of MK-0518B and ISENTRESS are

(b) (4)

VIROLOGY:

5) Please include a virology study report in Module 5 of the CTD for an integrated resistance analysis of LAM and RAL on pooled genotypic/phenotypic data collected from LAM/RAL-treated subjects in clinical trials referred to in the NDA for MK-0518B to support efficacy of MK-0518B.

Meeting Minutes
Meeting Type B

Merck response: Merck is of the opinion that the data from PN004 (Phase 2 study of raltegravir [RAL] + lamivudine [LAM] + tenofovir in treatment-naïve patients) would be the best source to provide such a report. Resistance was evaluated in PN004 and has been summarized in Section 11.3 of the CSR. The CSR will be included as a reference document as part of the filing. In addition, Merck will provide detailed longitudinal genotyping data documenting the kinetics of RAL and LAM resistance emergence in patients from PN004 who experienced virologic failure. These data will be included in a report and placed in Module 5, Section 5.3.5.4.

Merck does not believe it would be informative to include information from the treatment-experienced studies with RAL (PN005, PN018, PN019, PN055, PN022) because many of the patients entered these studies with documented LAM resistance at baseline. Additionally, in the switch studies (PN032 and PN033), no baseline resistance data are available since patients had viral loads below 50 copies/ml at enrollment, and resistance histories prior to enrollment for patients were incomplete. The presence of pre-existing LAM resistance, or lack of information about baseline resistance, confounds interpretation of resistance data for patients who experienced virologic failure in these treatment-experienced or switch studies.

Discussion: FDA stated that this approach is acceptable.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development,

Meeting Minutes
Meeting Type B

please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

Meeting Minutes
Meeting Type B

in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency’s regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency’s interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA’s finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in

Meeting Minutes
Meeting Type B

the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)

Meeting Minutes
Meeting Type B

<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

ATTACHMENTS AND HANDOUTS

FDA’s Preliminary Comments and Merck’s response

Question 1:

Does the Agency agree that the non-clinical safety package as outlined in the Background Package (Section 5) is adequate to support the filing and review of the NDA of MK-0518B?

FDA response: Yes, we agree that the non-clinical safety package is adequate to support the finding and review of the NDA of MK-0518B.

Question 2:

Does the Agency agree that the content and presentation of the clinical pharmacology program with supporting M&S data and in conjunction with the appropriate references to the NDA for EPIVIR[®] and P004 Study in the NDA for ISENTRESS[®] (MK-0518) will be adequate to support the filing and review of the NDA of MK-0518B as a 505(b)(2) application?

FDA response: Yes, we agree that the content and presentation of the clinical pharmacology program will support submission of the NDA as a 505(b)(2) application. The adequacy of the content of the NDA to support registration of MK-0518B will be evaluated during the review process.

Question 3:

Does the Agency agree that a separate Clinical Pharmacology and Biopharmaceutics Review Aid will not be required?

FDA response: Yes, we agree.

Question 4:

The Sponsor requests that the requirement for a 4 month safety update be waived. Does the Agency agree?

FDA response: Yes we agree.

Question 5:

Does the Agency agree that the proposal summarized in the Background Package (Section 9.4) will satisfy Office of Scientific Integration (OSI) requirements?

FDA response: Yes we agree.

Question 6:

Does the Agency concur with the submission plans for Case Report Tabulations (CRTs)?

FDA response:

- *Please submit the PK data that will be used to generate study report analyses for P071. In addition, if the datasets you plan to submit are not in SDTM format, please ensure that the structures, domains, and column names are similar across datasets. For example, column names for subject, trial number, treatment arm, etc. should be consistent across datasets, and dataset names (e.g. demographic, pharmacokinetic) should be consistent across studies.*

Merck Responses for Type B Pre-NDA Meeting

- *We agree that you do not have to submit safety files for the supportive trials in HIV-infected patients.*

Merck response: Yes, the Sponsor (Merck) will submit the PK data from P071.

Question 7:

Please confirm that submission of electronic Case Report Forms from Phase 1 studies for Categories 1 and 2 is sufficient for the NDA.

FDA response: In addition to submitting CRFs for patients who died or discontinued due to adverse events, please submit CRFs for patients who experienced serious adverse events.

Merck response: Since there were no subjects who died or who experienced serious adverse events in Phase 1 studies with MK-0518B, Merck plans to submit only CRFs for subjects who discontinued due to adverse events.

Question 8:

Does the Agency agree with the PSP proposed by the Sponsor?

FDA response: Yes, as stated in your November 01, 2013 communication, we agree with the submitted "Agreed Initial PSP". Please resubmit the PSP with your NDA.

Merck response: Yes, Merck will resubmit the PSP with the NDA.

Question 9:

Does the Agency agree with the approach to the development of MK-0518B label?

Yes, we agree. Please include only relevant information from the approved Isentress and Efavirenz labels to develop a streamlined MK-0518B label. A synopsis of clinical trial and safety information is sufficient. Please include referrals to the Isentress and Efavirenz labels as much as possible.

Merck response: Yes, Merck plans to include the relevant information and refer to the approved ISENTRESS® and EPIVIR® labels.

Question 10:

Does the Agency agree with the proposed plans for electronic submission?

FDA response: From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. However, please see additional comments below even though module 1 table of content was not provided...

- *Please include technical point of contact in your cover letter*
- *Providing a linked reviewer's aid/ reviewer's guide in module m1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, would be helpful to reviewers*

Merck Responses for Type B Pre-NDA Meeting

- *Provide sufficient bookmarks, linked table of contents and hyperlinks for ease of navigation Leaf titles, file names and bookmarks should be clear and indicative of the content. "meeting-bg-materials-appendix3.pdf" is not a clear file name*
- *Providing Table of Contents in 2.1, 3.1, 4.1 and 5.1, is not necessary in the eCTD structure. Please provide a reviewer's aid instead.*
- *The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.*
- *Providing a single 2.3.S, 2.3.P, 3.2.S and 3.2.P section with attribute of "ALL" and differentiating documents by leaf title, is acceptable. Additionally, indicating the substance/product/manufacture name at the beginning or end of a leaf title, helps sorting abilities.*

Merck response: Merck intends to author/publish the CMC section of the dossier (modules 2.3 and 3.2) in compliance with the ICH eCTD Specification V 3.2.2 and Guidance for Industry Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, leveraging drug product, drug substance, and manufacturer metadata to manage each drug substance/product as a unique section within the application.

- *Do not provide placeholders for sections that will not be submitted (e.g. 2.3.A, 5.3.1.3, N/A). Placeholders are only required when submitting ANDAs*
- *Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs)Pleasereferto:-
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>*

ADDITIONAL COMMENTS:

Chemistry, Manufacturing, and Controls:

1) The general recommendation for naming of antiviral products with multiple active ingredients is to list by alphabetical order. One exception is when one active ingredient is boosted by including a cytochrome P450 inhibitor; in that case the cytochrome inhibitor will be listed directly after the drug that is being boosted. For this combination, we recommend that the established name be lamivudine and raltegravir, 150 mg / 300 mg.

Merck response: Yes, Merck agrees to use the name lamivudine and raltegravir, 150 mg / 300 mg in critical sections such as the CMC section or the label. However, there might be some documents such as Phase 1 study CSRs that are finalized in which the order is raltegravir followed by lamivudine.

2) We concur that 12 months of long-term stability data at submission is appropriate for this product. We believe that this product could be used throughout the world, including countries in

Climatic Zone IVb (hot and very humid, e.g., Vietnam, Brazil). Please consider including the long-term condition of 30°C/75%RH in your stability studies, since stability under this condition is felt to support room temperature storage in all Climatic Zones.

Merck response: Merck appreciates the Agency's suggestions. However, the 30°C/75%RH study was not conducted for the intended commercial image. Merck will provide 12 month stability data at 25°C/60%RH and 6 months at 40°C/75%RH packaged in the intended commercial package configuration in the NDA. (b) (4)

BIOPHARMACEUTICS:

3) The dissolution data and information to be included in your NDA should conform to the following general guidelines:

I. **Dissolution Test:** Include the dissolution method development report supporting the selection of the proposed dissolution test for both components of your proposed drug product. The dissolution method development report should include the following information:

- a. Solubility data for the drug substances over the physiologic pH range;
- b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. The testing conditions should be clearly specified.

The dissolution profile should be complete and cover at least (b) (4) of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time- points*) is reached. We recommend use of at least twelve samples per testing variable;

- c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*);
- d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant manufacturing variables (*i.e., ± (b) (4) % change to the specification-ranges of these variables*). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent;
- e. Supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*).

Merck response: Merck will include the technical report of Development of the Dissolution Method in the submission.

II. **Dissolution Acceptance Criteria:** For the selection of the dissolution acceptance criteria of both components of your product, the following points should be considered:

Merck Responses for Type B Pre-NDA Meeting

- a. The dissolution profile data from the pivotal clinical batches (e.g. Phase 3 and bio-batches) and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification-sampling time point and specification value).
- b. The in vitro dissolution profile should encompass the timeframe over which at least $\frac{(b)}{(4)}$ % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- c. For immediate release product, the selection of the specification time point should be where $Q = \frac{(b)}{(4)}$ % dissolution occurs for each active component.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA review stage. However, the acceptability of the proposed dissolution criteria for your product will be made during the NDA review process based on the totality of the provided dissolution data.

Merck response: The acceptance criterion for the dissolution test will be established on the pivotal clinical batch (Biobatch) and registration stability batches.

CLINICAL PHARMACOLOGY:

- 4) Please ensure that previously characterized formulation-dependent interactions (e.g. antacids containing polyvalent cations) are evaluated using the to-be-marketed formulation.

Merck response: Drug-drug interactions (DDIs) that affect raltegravir PK can be roughly divided into those that affect raltegravir clearance (e.g., rifampin), and those that affect absorption (e.g., omeprazole, antacids). The DDIs that affect clearance would not be expected to be impacted by the differences in formulation or raltegravir PK profile between MK-0518B and the currently marketed ISENTRESS® formulation. DDIs that affect absorption may be affected by the differences in bioavailability and/or PK profile between MK-0518B and ISENTRESS® and can be further divided into 2 categories: 1) those that increase raltegravir PK due to increased absorption, and 2) those that decrease raltegravir PK due to interactions with metal cations. For DDIs in the first category (e.g., omeprazole, or other agents that may increase gastric pH and thus increase solubility of raltegravir), the magnitude of increase is bounded by increases in bioavailability, which cannot exceed 100%. Since the MK-0518B formulation has a higher bioavailability relative to the ISENTRESS® formulation, increases in raltegravir PK by this mechanism will be similar to or less than those observed with the ISENTRESS® formulation, and are thus not a concern for safety or efficacy of MK-0518B (for example, if the absolute bioavailability of ISENTRESS® is assumed to be ~30%, then an increase in bioavailability to 100% would result in an approximately 3-fold increase in AUC. The absolute bioavailability of the raltegravir component of MK-0518B would then be ~40%, and an increase in bioavailability to 100% would represent only a 2.5-fold increase in AUC). Therefore, Merck proposes that the labeling for MK-0518B will be consistent with the ISENTRESS® prescribing information, which recommends no dose adjustment for proton pump inhibitors and H2-blockers (e.g., omeprazole, famotidine).

For interactions related to metal cations (e.g., antacids), the interaction is likely to be a function of both gastric pH and the active ingredient (raltegravir), rather than formulation composition.

Merck Responses for Type B Pre-NDA Meeting

The differences in PK profile between MK-0518B and ISENTRESS® are small enough that it is unlikely that a larger interaction will be observed between metal cations and MK-0518B, but it is possible that a similar interaction would be observed. Therefore, Merck proposes that the labeling for MK-0518B will state “Coadministration of TRADEMARK with aluminum and/or magnesium-containing antacids is not recommended. When TRADEMARK is coadministered with calcium carbonate-containing antacids, no dosage adjustment is recommended”, which is consistent with the ISENTRESS® prescribing information.

VIROLOGY:

5) Please include a virology study report in Module 5 of the CTD for an integrated resistance analysis of LAM and RAL on pooled genotypic/phenotypic data collected from LAM/RAL-treated subjects in clinical trials referred to in the NDA for MK-0518B to support efficacy of MK-0518B.

Merck response: Merck is of the opinion that the data from PN004 (Phase 2 study of raltegravir [RAL] + lamivudine [LAM] + tenofovir in treatment-naïve patients) would be the best source to provide such a report. Resistance was evaluated in PN004 and has been summarized in Section 11.3 of the CSR. The CSR will be included as a reference document as part of the filing. In addition, Merck will provide detailed longitudinal genotyping data documenting the kinetics of RAL and LAM resistance emergence in patients from PN004 who experienced virologic failure. These data will be included in a report and placed in Module 5, Section 5.3.5.4.

Merck does not believe it would be informative to include information from the treatment-experienced studies with RAL (PN005, PN018, PN019, PN055, PN022) because many of the patients entered these studies with documented LAM resistance at baseline. Additionally, in the switch studies (PN032 and PN033), no baseline resistance data are available since patients had viral loads below 50 copies/ml at enrollment, and resistance histories prior to enrollment for patients were incomplete. The presence of pre-existing LAM resistance, or lack of information about baseline resistance, confounds interpretation of resistance data for patients who experienced virologic failure in these treatment-experienced or switch studies.

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
12/02/2013

MK-0518B LAMIVUDINE/RALTEGRAVIR FDC
1.6.3 Correspondence Regarding Meetings

FDA Confirmation of Type C Meeting Cancellation was received on 14-May-2012.



IND 113176

MEETING REQUEST CANCELLED

Merck Sharp & Dohme Corp.
Attention: Robert A. Fromtling, Ph.D.
Director, Global Regulatory Affairs
P.O. Box 2000 -RY33-212
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0518B (raltegravir potassium/lamivudine) Fixed-Dose Combination (FDC) Tablet.

We also refer to your April 18, 2012 electronic mail communication requesting cancellation of the meeting we scheduled on April 19, 2012 in response to your Type C meeting request because the FDA's preliminary comments sufficiently provided guidance on the proposed development plans for MK-0518B. The April 19, 2012 meeting has been cancelled.

If you have any questions, call Mammah Sia Borbor, M.S., M.B.A., Regulatory Project Manager, at (301) 796-7731 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

MAMMAH S BORBOR
05/04/2012

MK-0518B LAMIVUDINE/RALTEGRAVIR FDC

1.6.3 Correspondence Regarding Meetings

FDA Preliminary Comments for Type C meeting were received on 18-Apr-2012. These comments were sufficient to cancel the planned Type C meeting scheduled for 19-Apr- 2012.



IND 113176

MEETING PRELIMINARY COMMENTS

Merck Sharp & Dohme Corp.
Attention: Robert A. Fromtling, Ph.D.
Director, Global Regulatory Affairs
P.O. Box 2000 -RY33-212
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0518B (raltegravir potassium/lamivudine) Fixed-Dose Combination (FDC) Tablet.

We also refer to your February 10, 2012, correspondence, received February 10, 2012 requesting a meeting to discuss the proposed development plans for MK-0518B, including the acceptability of submitting a new NDA for this FDC based on a relative bioavailability/bioequivalence Phase 1 trial.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 19, 2012, 12:30 PM to 1:30 PM, EST, via teleconference between Merck Sharp & Dohme Corp. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Your questions are in bold font and the DAVP's preliminary responses are in italic.

Question 1

Merck Sharp & Dohme Corp. consider the 3 proposed Phase I studies, including a pivotal relative bioavailability/bioequivalence study, a raltegravir/lamivudine pharmacokinetic drug interaction study and a food-effect study, provided they meet targeted endpoints, sufficient to bridge all safety and efficacy data from the ISENTRESS® and EPIVIR® programs to MK-0518B. Does the Agency concur?

DAVP's Response:

The proposed trials are reasonable, however it is not clear what additional information a DDI trial will provide based on the following:

- 1. Differences in the route of elimination: Raltegravir is primarily metabolized via UGT1A1 mediated glucuronidation pathways and is not a substrate of CYP enzymes. Lamivudine is eliminated unchanged in urine by active organic cationic secretion.*
- 2. The package insert of raltegravir indicates that in drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of lamivudine.*

Although the pharmacokinetics of raltegravir (when given alone) and lamivudine (when given alone) has not been determined in the development program of MK-0518B, available information from MK-0518B and raltegravir development programs, literature, and other sources can be used to determine the potential for an interaction between raltegravir and lamivudine. Hence, based on the well-characterized elimination routes of both drugs and the availability of reference PK values, we do not believe that conducting a formal drug-drug interaction trial between raltegravir and lamivudine will provide additional information.

Question 2a

Plasma trough concentrations (C_{12hr}) for raltegravir are considered to be a clinically relevant pharmacokinetic endpoint based on the extensive PK/PD and M&S analyses performed from Phase III data (P071), where the safety, efficacy and pharmacokinetics after 48-weeks of treatment with ISENTRESS® 400 mg twice daily and ISENTRESS® 800 mg once daily were compared. Therefore, Merck Sharp & Dohme Corp. proposes the AUC_{0-t} and C_{12hr} , but not C_{max} , for raltegravir be considered as the primary pharmacokinetic endpoints for raltegravir in the pivotal relative bioavailability/bioequivalence study. Does the Agency concur?

DAVP's Response:

It is acceptable to use AUC_{0-t} and C_{12hr} as the primary pharmacokinetic endpoints.

The review team recommends keeping C_{max} as a primary endpoint. In the event

that the estimate and/or confidence interval of the ratio of RAL C_{max} is outside the standard "no-effect" bounds, supportive safety data can be provided.

Question 2b

If the proposal to use C_{12hr} for raltegravir is acceptable to the Agency, the Applicant proposes that the comparability bounds be as follows: (90% CI of the GMR [MK-0518B/co-administration] of the C_{12hr} for raltegravir of (0.80, 2.00). Does the Agency concur?

DAVP's Response:

The proposal to use the "0.8-2.00" comparability bounds for C_{12hr} is acceptable.

Question 3

a. Merck Sharp & Dohme Corp. considers that 3 proposed Phase 1 clinical trials will be sufficient to support the registration of MK-0518B for the proposed indication, and that an additional clinical trial with MK-0518B will not be required to support registration. If these Phase 1 clinical trials do not meet the targeted endpoints for bridging as outlined in Questions 1 and 2, then Merck Sharp & Dohme Corp. would propose

(b) (4)

(b) (4)

DAVP's Response for Question 3a and 3b:

(b) (4)

(b) (4). *Exposure-response (safety and/or efficacy) data from the individual development programs of raltegravir and lamivudine may be utilized to provide supportive information for exposure changes which fall outside the standard "no effect" bounds. The Division encourages follow up discussion if the data from the proposed BA/BE, DDI (if conducted, see response to Question 1), and food effect trials suggest the need for further evaluation.*

Question 4

(b) (4)

Question 5

Considering that both ISENTRESS® and EPIVIR® are recommended to be given without regard to food, the pivotal relative bioavailability/bioequivalence study proposed by the Applicant will be conducted in the fasted state. Does the Agency concur?

DAVP's Response:

The proposed approach of conducting the pivotal relative BA/BE study under fasted conditions is acceptable.

Question 6

An impurity specification of \leq (b) (4) % has been proposed for (b) (4) an impurity in the lamivudine component of MK-0518B. Based on the existence of abundant preclinical toxicity data in the scientific literature (b) (4) (b) (4) existing literature is adequate to qualify the impurity at \leq (b) (4) % and additional preclinical studies are not necessary. Does the Agency concur?

DAVP's Response:

Yes, we concur.

Question 7

Given that there is no common or suspected synergistic target organ toxicity or concern for an interaction between raltegravir and lamivudine and both are currently approved compounds, according to appropriate regulatory guidances, nonclinical studies with co-administration of raltegravir and lamivudine are not considered to be required. Does the Agency concur?

DAVP's Response:

Yes, we concur.

Additional Comments:

Chemistry, Manufacturing and Control

1. Please comment if there is an issue (b) (4) as it pertains to the USP monograph for lamivudine, e.g. a) water content <921 > and b) Identification by IR <197M>. Please discuss whether you have plans to petition USP for change in the monograph for lamivudine drug substance.

Biometrics

2. CDER strongly encourages sponsors/applicants to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

If you have any questions, call Mammah Sia Borbor, M.S., M.B.A., Regulatory Project Manager, at (301) 796-7731 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Mammah Sia Borbor, M.S., M.B.A.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

MAMMAH S BORBOR
04/18/2012