CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205786Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205786 SUPPL # Original HFD # 530

Trade Name Isentress for oral suspension

Generic Name raltegravir

Applicant Name Merck Sharp & Dohme Corp.

Approval Date, If Known December 20, 2013

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

NDA 205786: 505(b)(1) Original (new pediatric dosage form)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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 22145 Isentress (raltegravir) film-coated tablets

NDA# NDA 203045 Isentress (raltegravir) chewable tablets

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

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

IMPAACT P1066 (also known as Merck P022), cohorts IV and V (4 weeks to < 2 years of age)

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.")

IMPAACT P1066 (cohorts IV and V) YES ☐ NO ☒

Note: P1066 was used to support the approval of NDA 203045 for Isentress chewable tablets (patients ages 2 to less than 12, cohorts II and III). However, the data submitted in the current application, NDA 205786, have never been reviewed by the Agency and were generated with a new dosage form (Isentress for oral suspension) in a new pediatric age group (patients 4 weeks (b) (4) *, cohorts IV and V). Therefore, the investigation can be considered "new."*

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?

IMPAACT P1066 (cohorts IV and V) 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"):

IMPAACT P1066 (cohorts IV and V)

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?

IMPAACT P1066

IND # 77,787 YES ☐ NO ☒

Explain:
The Division of AIDS of the National Institute of Allergy and Infectious Disease, NIH is the sponsor of IND 77,787 under which IMPAACT P1066 is being conducted

(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?

IMPAACT P1066	!
	!
YES ☒	! NO ☐
Explain:	! Explain:
The applicant certified that it provided substantial support for the study.	
(b) (4)	

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Katherine Schumann, M.S.
Title: Regulatory Project Manager
Date: December 18, 2013

Name of Office/Division Director signing form: Jeffrey Murray, M.D., M.P.H.
Title: Deputy Director, Division of Antiviral Products
Date: December 20, 2013

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/

KATHERINE SCHUMANN
12/20/2013

JEFFREY S MURRAY
12/20/2013

Raltegravir Potassium Tablets
Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Ursula Marek

6/13/13

Ursula Marek, Pharm.D.
Associate Director
Global Regulatory Affairs

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA #	NDA Supplement #	If NDA, Efficacy Supplement Type:
205786 22145 203045	S-000 (Original NDA) S-031 S-009	N/A SE-8 SE-8

Proprietary Name: Isentress
Established/Proper Name: raltegravir
Dosage Form:
NDA 205786: for oral suspension, 100 mg
NDA 22145 S-031: tablets, 400 mg
NDA 203045 S-009: chewable tablets, 25 mg and 100 mg

Applicant: Merck Sharp and Dohme Crop.
Agent for Applicant (if applicable): N/A

RPM: Katherine Schumann, M.S.

Division: Division of Antiviral Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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.

❖ Actions

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (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., nrew listed drug, patent certification revised).

• Proposed action User Fee Goal Date is NDA 205786: December 27, 2013 sNDAs 22145/203045: December 26, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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 _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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 (*see comment*)

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

Comments: **One cohort still outstanding (pediatric patients 0 to 4 weeks) to fulfill Pediatric Written Request**

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No

[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.

• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review	☐ N/A (no paragraph IV certification) ☐ Verified

documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*

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

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

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

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

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

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as ☐ Yes ☐ No

provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): Approval, December 20, 2013

[4] Fill in blanks with dates of reviews, letters, etc.

Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	December 19, 2013
• Original applicant-proposed labeling	June 27, 2013
• Example of class labeling, if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	December 19, 2013
• Original applicant-proposed labeling	June 27, 2013
• Example of class labeling, if applicable	Tivicay (dolutegravir) August 12, 2013
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	December 13, 2013 (chewable tablets) December 19, 2013 (oral suspension)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM December 20, 2013 ☒ DMEPA October 1, 2013 ☒ DMPP/PLT (DRISK) November 22, 2013 ☒ OPDP (DDMAC) November 22, 2013 ☒ SEALD December 12, 2013 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review, August 7, 2013 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included NDA 205786, December 20, 2013 NDA 22145 S-031 / NDA 203045 S-009, December 20, 2013

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC November 6, 2013 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None December 12, 2013
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Refer to CDTL review dated December 12, 2013
• Clinical review(s) *(indicate date for each review)*	Clinical Review: December 2, 2013

[6] Filing reviews should be filed with the discipline reviews.

	Filing Review: August 14, 2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Please refer to Page 10 of the clinical review dated December 2, 2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☒ None N/A
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested Refer to clinical pharmacology inspection review summary
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None November 7, 2013 Filing Review: August 2, 2013
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None December 12, 2013
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None November 6, 2013 Filing Review: August 6, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None November 14, 2013

Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Product Quality: Addendum 2: December 19, 2013 Addendum 1: December 11, 2013 Review: November 18, 2013 Filing Review: September 19, 2013 Biopharmaceutics: November 18, 2013 Filing Review: August 2, 2013
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed July 22, 2013 - Microbiology assessment at filing found to be acceptable
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Refer to pages 63-64 of November 18, 2013 product quality review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ 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) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: October 3, 2013 ☒ Acceptable Refer to pages 67-70 of November 18, 2013 product quality review for EER printouts ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

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

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

KATHERINE SCHUMANN
12/27/2013

From: Schumann, Katherine
To: "Abeygunawardana, Chitrananda"
Subject: RE: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI
Date: Tuesday, December 17, 2013 1:00:00 PM
Attachments: image001.png

Abey,

I have consulted with the review team and they acknowledge that there are two definitions for the geometric CV and accept the formula and updated Table 9 presented below. However, they would like to retain the table title as follows:

Table 9: Raltegravir Steady State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Doses

Please let me know if you have any further questions.

Warm Regards,
Katie

From: Abeygunawardana, Chitrananda [mailto:abey@merck.com]
Sent: Tuesday, December 17, 2013 11:35 AM
To: Schumann, Katherine
Cc: Abeygunawardana, Chitrananda
Subject: FW: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI
Importance: High

Hi Katie,

Regarding the revisions you communicated yesterday on the PK table (Table 9), Merck accepts suggestion to including the geometric CV% and proposes the following revisions:

REVISED TABLE

Table 9: Raltegravir Steady State Pharmacokinetic Parameters Following Administration of Recommended Doses

Body Weight	Formulation	Dose	N*	Geometric Mean (%CV†) $AUC_{0\text{-}12hr}$ (µM•hr)	Geometric Mean (%CV†) C_{12hr} (nM)
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 (121%)	233 (157%)
≥25 kg	Chewable tablet	Weight based dosing, see Table 1	9	22.1 (36%)	113 (80%)
11 - 25 kg	Chewable tablet	Weight based dosing, see Table 2	13	18.6 (68%)	82 (123%)
3 – 20 kg	Granules for suspension	Weight based dosing, see Table 2	19	24.5 (43%)	113 (69%)

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric coefficient of variation.

Rationale:

Merck acknowledges that there are two definitions for the geometric CV, that provided by the FDA and that which we use. However, the formula that used by Merck is more common, and is the output provided in many PK and statistical programs. In addition, this formula has a theoretical basis, and can be derived, while the one proposed by the FDA does not have a theoretical root.

In the table above, the numbers are recalculated using the following definition of the GeoCV:

(b) (4)

Could you please let me know if this is acceptable to the agency? Thanks,

Abey

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Monday, December 16, 2013 4:47 PM
To: Abeygunawardana, Chitrananda
Subject: RE: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI

Abey,

Please find attached the Division's comments on section 12.3 and one additional request regarding the nomenclature for the granules.

I understand the nomenclature may be an issue at this point in the review. If you are unable to resubmit the carton and container labels this week but agree to make the change, we can approve the labels submitted on Friday but stipulate the agreed-upon change in the approval letter.

I will give you a call in 5-10 minutes.

Warm Regards,
Katie

From: Abeygunawardana, Chitrananda [mailto:abey@merck.com]
Sent: Monday, December 16, 2013 4:13 PM
To: Schumann, Katherine
Subject: RE: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI

OK Thanks.

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Monday, December 16, 2013 4:09 PM
To: Abeygunawardana, Chitrananda
Subject: RE: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI

I should have them for you within a half hour. I will call after sending.

Katie

From: Abeygunawardana, Chitrananda [mailto:abey@merck.com]
Sent: Monday, December 16, 2013 4:03 PM
To: Schumann, Katherine
Subject: RE: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI

Hi Katie,

When should we expect additional comments?
Please give me a call if you have a time. Thanks,

Abey

From: Abeygunawardana, Chitrananda
Sent: Friday, December 13, 2013 9:48 PM
To: 'Schumann, Katherine'

Subject: RE: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI

Thanks Katie,

I have forwarded labeling comments to the team.
I assume we will be getting additional comments early in the week so we could address all comments and resubmit the label once.
Yes, we can discuss the details and timing on Monday.

Thanks and have a nice weekend!
Abey

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Friday, December 13, 2013 8:46 PM
To: Abeygunawardana, Chitrananda
Subject: NDA 205786 Isentress (b) (4) suspension - Additional Comments regarding PI

Dear Abey,

Please find attached the Isentress PI with additional comments from DAVP. Please note we have made edits to Section 2 and Section 17 following input from the OND labeling review team (SEALD).

We plan to provide additional comments on Section 12.3, including Table 9, following review of the data sent earlier today.

Regarding the CD4 analyses in Section 14, the Division agrees to the numbers that Merck originally proposed.

Please let me know if you have any questions. I will contact you on Monday to discuss the timeline for re-submission of labeling.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
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<GFS PK Tables Updated.docx>

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KATHERINE SCHUMANN
12/20/2013

From: Schumann, Katherine
To: Abeygunawardana, Chitrananda (abey@merck.com)
Subject: Isentress PPI and IFU
Date: Tuesday, December 17, 2013 1:28:00 PM
Attachments: 2013_12_17 marked_09-wrm-ifu-mk0518-mf-(b) (4)-susp.doc
2013_12_17 marked_09-wrm-ppi-mk0518-mf(b) (4)-susp.doc

Dear Abey,

There are several additional, very minor comments on the patient labeling following review of the PPI and IFU you sent on December 10. The patient labeling group has added them to your track-changes versions of the documents.

Please see the two attached documents. I hope that these are straightforward enough that you have time to consider them as you are revising the document to change the nomenclature. Please let me know if you have any questions.

Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
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KATHERINE SCHUMANN
12/20/2013

From: Schumann, Katherine
To: Abeygunawardana, Chitrananda (abey@merck.com)
Subject: NDA 205786 Isentress [redacted] (b) (4) suspension - Additional Comments regarding PI
Date: Friday, December 13, 2013 8:45:00 PM
Attachments: 2013_12_13 Isentress DAVP edits.doc

Dear Abey,

Please find attached the Isentress PI with additional comments from DAVP. Please note we have made edits to Section 2 and Section 17 following input from the OND labeling review team (SEALD).

We plan to provide additional comments on Section 12.3, including Table 9, following review of the data sent earlier today.

Regarding the CD4 analyses in Section 14, the Division agrees to the numbers that Merck originally proposed.

Please let me know if you have any questions. I will contact you on Monday to discuss the timeline for re-submission of labeling.

Warm Regards,
Katie

Katherine Schumann, M.S.
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FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
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KATHERINE SCHUMANN
12/20/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir) (b) (4) suspension**
Isentress (raltegravir) tablets
Isentress (raltegravir) chewable tablets

Date: **December 16, 2013**

To: **Chitrananda Abeygunawardana, PhD, Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 – Comments Regarding Draft Prescribing Information (PI)**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) suspension and your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir) tablets and chewable tablets. We also refer to your December 10, 2013 submission of the draft prescribing information (PI).

1. To bring the nomenclature for Isentress into concordance with USP guidelines, please revise the product title throughout your labeling (package insert, patient information, instructions for use and carton/container labels) by removing the word (b) (4) and adding the word "oral" as follows:

   ISENTRESS® (raltegravir) (b) (4) for oral suspension

   The product title should instead read:

   ISENTRESS® (raltegravir) for oral suspension

2. In Section 12.3 we have additional changes:
   a) The data from Cohort III is not of sufficient sample size to determine that the overall lower trough exposures would not result in an incremental decrease in efficacy. Therefore, revise the paragraph below as follows:

   Overall, dosing in pediatric patients achieved exposures (C_{trough}) above 45 nM in the majority of subjects, but some differences in exposures between formulations were observed. Pediatric patients above 25 kg administered the chewable tablets had lower trough concentrations (113 nM) compared to pediatric patients above 25 kg administered the 400 mg tablet formulation (233 nM) *[see Clinical Studies (14.3)]*. As a result, the 400 mg film-coated tablet is the recommended dose in patients weighing at least 25 kg; however, the chewable tablet offers an alternative regimen in patients weighing at least 25 kg who are unable to swallow the film-coated tablet *[see Dosage and Administration (2.3)]*. In addition, pediatric patients weighing 11 to 25 kg who were administered the chewable tablets had the lowest trough concentrations (82 nM) compared to all other pediatric subgroups. (b) (4) .

   b) Table 9, we have changed the provided %CVs to reflect geometric coefficient of variations rather than arithmetic coefficient of variations. As all values in the table have been recalculated from the original version and as the PK parameters are presented as geometric means, we feel it is more appropriate to update the %CVs, too.

   Please revise the table as follows (changes displayed in red font):

Table 9: Raltegravir Steady State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Doses

Body Weight	Formulation	Dose	N*	Geometric Mean (%CV†) $AUC_{0\text{-}12hr}$ (μM•hr)	Geometric Mean (%CV†) C_{12hr} (nM)
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 ((b) (4))	233 ((b) (4)%)
≥25 kg	Chewable tablet	Weight based dosing, see Table 1	9	22.1 ((b) (4)%)	113 ((b) (4)%)
11 to less than 25 kg	Chewable tablet	Weight based dosing, see Table 2	13	18.6 ((b) (4)%)	82 ((b) (4)%)
3 to less than 20 kg	Granules for suspension	Weight based dosing, see Table 2	19	24.5 ((b) (4)%)	113 ((b) (4)%)

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric Coefficient of variation.

Please resubmit the labeling to address the above comments by close of business on **Wednesday, December 18, 2013**.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

_____

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

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/s/

KATHERINE SCHUMANN
12/16/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir) (b) (4) suspension**
Isentress (raltegravir) tablets
Isentress (raltegravir) chewable tablets

Date: **November 27, 2013**

To: **Chitrananda Abeygunawardana, PhD, Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 – Comments Regarding Draft Prescribing Information (PI), Patient Prescribing Information (PPI) and Instructions for Use (IFU)**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) suspension and your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir) tablets and chewable tablets. We also refer to your November 21, 2013 submission of the draft prescribing information (PI) in response to our comments of November 8, 2013 and discussion held during the November 15, 2013 teleconference.

The attached comments regarding the proposed Isentress PI, PPI, and IFU are being conveyed to you on behalf of the review team.

Please submit your response by December 6, 2013.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience.

Katherine Schumann, M.S.
Regulatory Project Manager

Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosed: Isentress PI, PPI and IFU

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KATHERINE SCHUMANN
11/27/2013

PeRC PREA Subcommittee Meeting Minutes
November 6, 2013

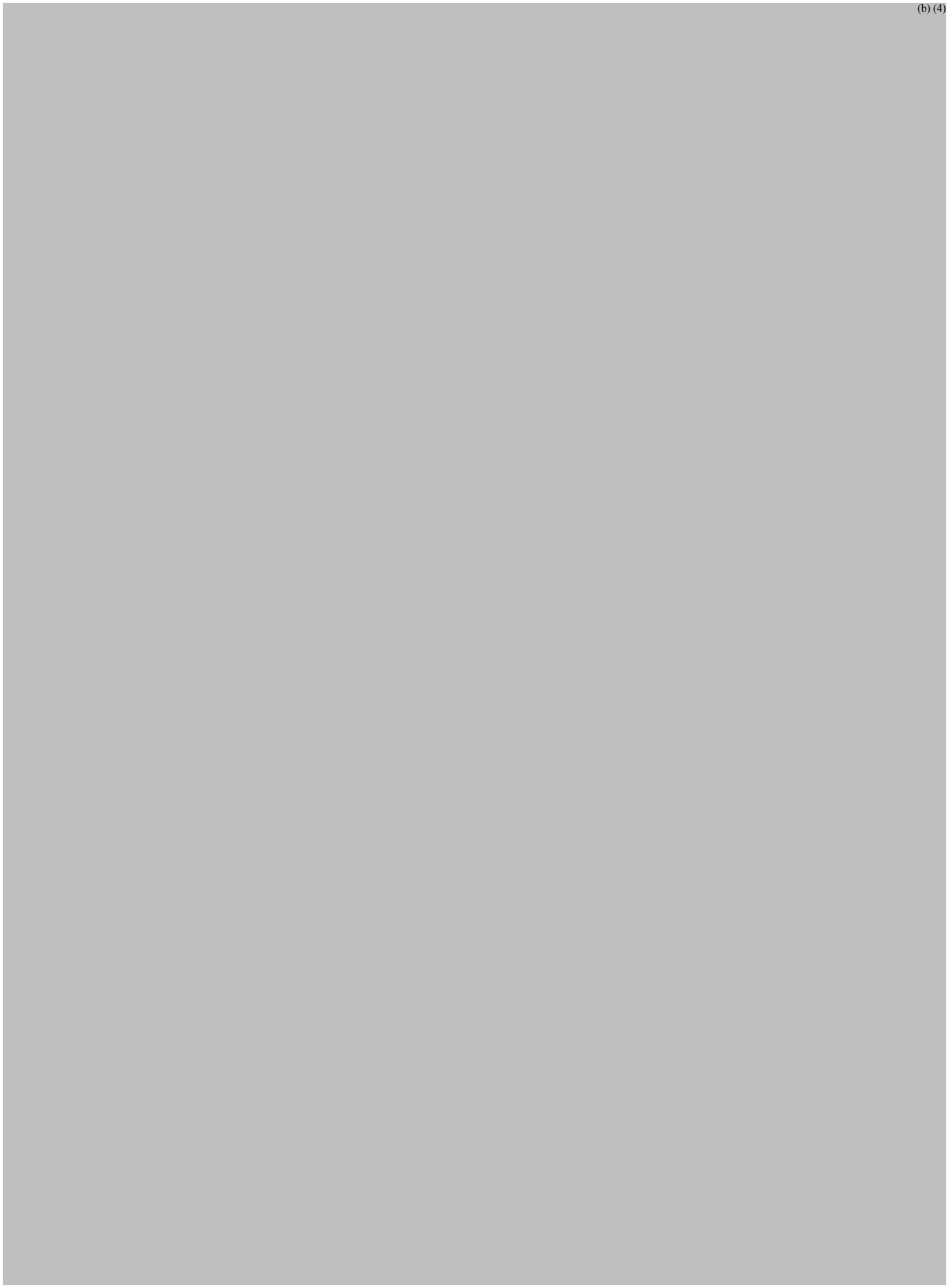
PeRC Members Attending:
Lynne Yao
Robert Nelson
Hari Cheryl Sachs
Karen Davis-Bruno
Rosemary Addy
Patricia Dinndorf
Julia Pinto
William J. Rodriguez
Peter Starke
Wiley Chambers
Lily Mulugeta
Daiva Shetty
Andrew Mosholder
Gregory Reaman
Barbara Buch
Martha Nguyen
Dianne Murphy
Jane Inglese

Guests Attending:
Nichella Simms (PMHS)
Erica Radden (PMHS)
Donna Snyder (PMHS)
Kimberly Compton (DAAAP)
Ellen Fields (DAAAP)
Srikanth Nallani (DAAAP)
Sofia Chaudhry (DPARP)
Susan Limb (DRPAR)
Satjit Brar (OCP)
Sandy Chang (DPP)
Glenn Mannheim (DPP)
Jing Ahang (DPP)
Lawren Slate (OCP)
Carla Epps (DGIEP)
David Joseph (DGIEP)
Rigo Roca (DAAAP)
William Chong (DMEP)
Todd Bourcier (DMEP)
Josh Lloyd (DAAAP)
Mukesh Summan (DMEP)
Swati Patwardhan (DAAAP)
Brittany Goldberg (DAVP)
Katherine Schumann (DAVP)
Yodit Belew (DAVP)
Karen M. Mahoney (DMEP)
Manoj Khurana (OCP)
Lokesh Jain (OCP)

Agenda

11:00	NDA	(b) (4)
11:15	NDA	
11:30	NDA	205786/ 22145 Isentress (raltegravir) Assesement
11:45	NDA	(b) (4)
	NDA	
	NDA	

(b) (4)


(b) (4)

Isentress (raltegravir) Assessment

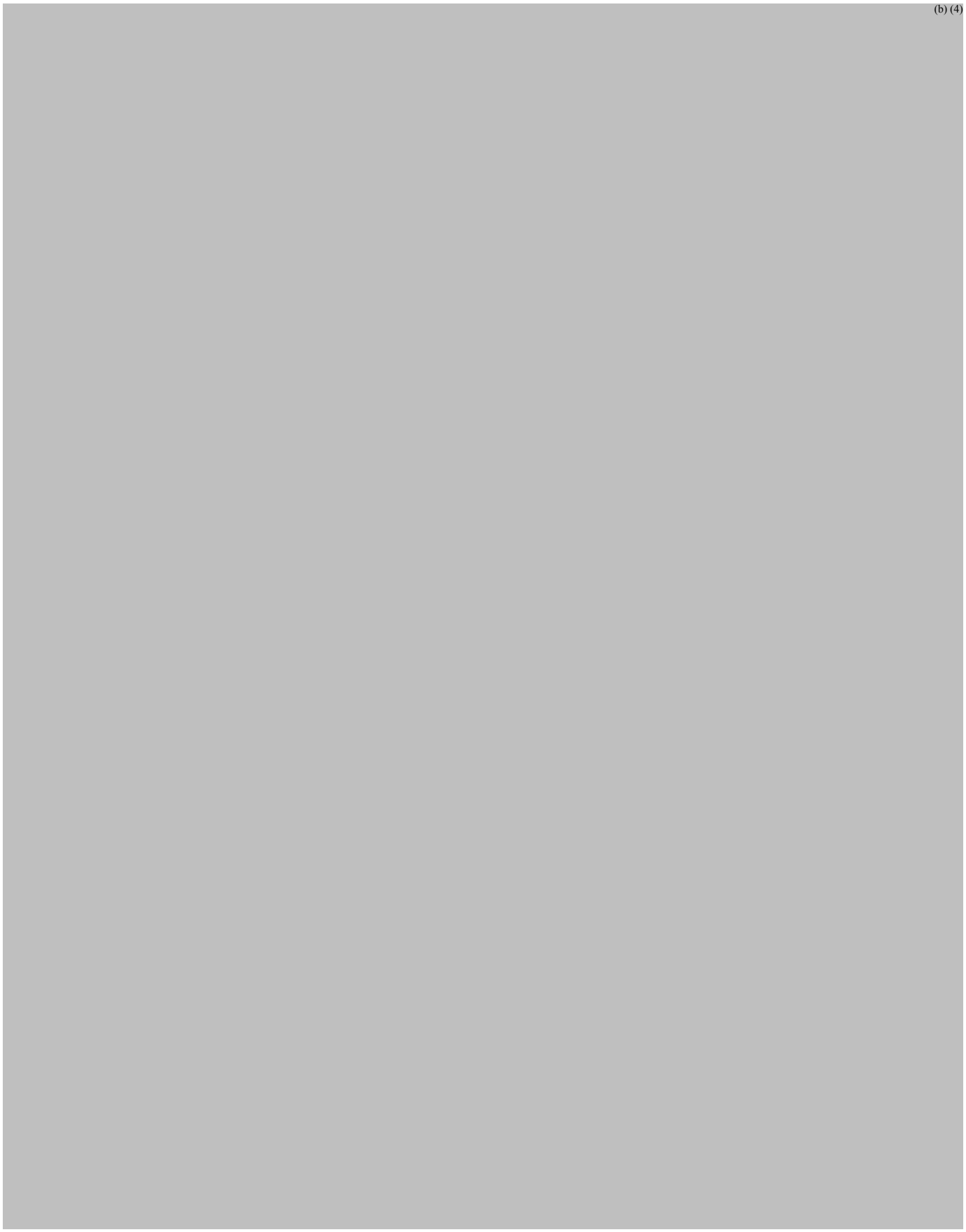
- NDA 205786 seeks marketing approval for Isentress (raltegravir) (b) (4) suspension for the treatment of HIV-1 infection in combination with other antiretroviral agents in pediatric patients aged 4 weeks (b) (4).
- The application was resubmitted on June 26, 2013, and has a PDUFA goal date of December 26, 2013.
- The application triggers PREA as directed to a new dosage form.
- The application was submitted in response to the following PREA PMR for NDA 22145 S-031 (raltegravir film-coated tablets) and NDA 203045 S-009 (raltegravir chewable tablets):
    - A deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 4 weeks to 2 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.
    - Study due date: 01/05/2015.
- (b) (4)
- A waiver is being requested for pediatric patients 2 to 18 years because the product fails to represent a meaningful therapeutic benefit over existing therapies for this age group and is unlikely to be used in a substantial number of all pediatric patients of this age.
- *Division justification for waiver:* The product (raltegravir granules for suspension) does not represent a meaningful therapeutic benefit over existing therapies (film-coated tablets and chewable tablets) for pediatric patients ages 2 to 18 years and is unlikely to be used in a substantial number of pediatric patients in this age group. As the three dosage forms (tablets, chewable tablets and granules) are not bioequivalent,

the Division is not proposing to indicate the granules for suspension for children above 2 years of age.

- (b) (4)

- *PeRC Recommendations:*
  - The PeRC agreed with the pediatric assessment for patients aged 4 weeks (b) (4) (b) (4).
  - The PeRC agreed with the previous assessment for pediatric patients 2 to 18 years of age. Labeling is adequate for this age group.
  - (b) (4)

(b) (4)


(b) (4)

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/s/

JANE E INGLESE
11/18/2013

Cuff, Althea

From: Cuff, Althea
Sent: Tuesday, November 12, 2013 10:16 AM
To: abey@merck.com
Subject: FW: NDA 205786 - Information Request

Dear Abey,

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) (b) (4) suspension Please respond by Friday November 15, 2013.

1. We have evaluated your proposal for not including (b) (4) in the product specification. For uniform patient dosing of a granule for suspension drug product, a (b) (4) granule should be maintained. At this time, only limited data from commercial scale batches are available to support (b) (4) well controlled in the drug product through end of product shelf-life. Therefore, include a test (b) (4) in the drug product specification and propose a suitable acceptance criterion. As additional commercial scale product manufacturing and stability experience are gained post-marketing, it may be feasible to request deletion of the test if adequately supported by a sufficient body of data.

2. We acknowledge you response to question #3 in the Agency Information Request letter dated 8/14/2013. We note that fineness of dispersion is a relevant quality attribute to the youngest patient population this drug product is intended for, 4 week infants. Therefore, include a “fineness of dispersion” test in the drug product specification.

3. Observed darkening of the granules over stability is attributed to banana flavor. Please elaborate. Is it due to (b) (4)?

Thanks, Althea

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/s/

ALTHEA CUFF
11/12/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir) (b) (4) suspension**
Isentress (raltegravir) tablets
Isentress (raltegravir) chewable tablets

Date: **November 8, 2013**

To: **Chitrananda Abeygunawardana, PhD, Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 – Comments Regarding Draft Prescribing Information (PI)**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) suspension and your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir) tablets and chewable tablets. We also refer to your November 5, 2013 submission of the draft prescribing information (PI) in response to our comments of October 28, 2013.

The attached comments regarding the proposed Isentress PI are being conveyed to you on behalf of the review team.

Please note that the DAVP has revised the Indications and Usage section of the PI to remove the (b) (4)," as well as the details of studies that describe the basis for approval. Current internal guidance within CDER recommends that the details of studies that describe the bases for approval not be included in the Indications and Usage section, but instead described in the Clinical Studies section. Additionally, review Divisions are being encouraged to exclude information regarding specific subgroups (e.g. pediatric patients) in the Indications and Usage section unless a specific safety concern or a lack of effectiveness has been demonstrated, or a particular limitation of use applies. Specifics

regarding the patient population studied should be described in the Clinical Studies section of the labeling. In this context, DAVP has determined it is not necessary to describe use of raltegravir in pediatric patients as a distinct indication statement.

We are also providing a chart below containing Subject IDs for each efficacy category in support of DAVP's revisions to the Clinical Studies section of the PI.

Please respond with revised labeling by Tuesday, November 12, 2013. This can be an informal correspondence via email, followed by a formal submission to the NDA and sNDAs.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

_____

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

Week 24					
	HIV RNA <50	HIV RNA <400	HIV RNA >50	HIV RNA >400	No Data
Subject ID	461310	801537	801537	382192	1270100
	801526	2020158	2020158	801399	
	801528	2020161	2020161	801525	
	801531	2020176	2020176	801538	
	801532	8504486	8504486	2020164	
	801535	461310	382192	2020171	
	801536	801526	801399	8501394	
	2020159	801528	801525	8501806	
	8504252	801531	801538		
		801532	2020164		
		801535	2020171		
		801536	8501394		
		2020159	8501806		
		8504252			
Week 48					
	HIV RNA <50	HIV RNA <400	HIV RNA >50	HIV RNA >400	No Data
Subject ID	461310	801531	801531	382192	801538
	801399	801536	801536	801525	1270100
	801526	2020161	2020161	801535	2020171
	801528	8501394	8501394	2020164	
	801532	461310	382192	2020176	
	801537	801399	801525	8501806	
	2020158	801526	801535		
	2020159	801528	2020164		
	8504252	801532	2020176		
	8504486	801537	8501806		
		2020158			
		2020159			
		8504252			
		8504486			

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/s/

KATHERINE SCHUMANN
11/08/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir) (b) (4) suspension**
Isentress (raltegravir) tablets
Isentress (raltegravir) chewable tablets

Date: **October 28, 2013**

To: **Chitrananda Abeygunawardana, PhD, Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 – Comments Regarding Draft Prescribing Information (PI)**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) suspension and your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir) tablets and chewable tablets. We also refer to your August 19, 2013 submission of the draft prescribing information (PI).

The attached comments regarding the proposed Isentress prescribing information are being conveyed to you on behalf of the review team. Please note that comments on the PPI will be forthcoming at a later date.

Please respond with a re-submission of the PI by November 5, 2013.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

KATHERINE SCHUMANN
10/28/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir) (b) (4) suspension**
Isentress (raltegravir) tablets
Isentress (raltegravir) chewable tablets

Date: **October 18, 2013**

To: **Ursula Marek, Pharm.D., Associate Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 – Additional Comments Regarding Instructions for Use**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) suspension and your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir) tablets and chewable tablets. We also refer to your September 6, 2013 response to our August 13, 2013 initial comments on the Instructions for Use (IFU) document.

The review team is providing the following additional comments regarding the revised IFU.

1. Re-design IFU so that the sequential steps appear in 1 vertical column. The text should go horizontally across the page and not in a narrow column alongside each figure.

2. Present the information such that each corresponding figure either immediately follows below the step, or is next to it.

3. Move the instruction "For each dose of ISENTRESS (b) (4) Suspension you will need the following" so that it follows the instruction and figure describing the supplies provided in the kit.

4. In steps 2, 4, and 8, revise the figure to show the other hand steadying the syringe barrel. Inexperienced users are unlikely to manipulate a syringe with 1 hand.

5. In Figure I: To ensure that patients prepare the dose that is prescribed instead of the dose that is presented in Figure I, please add the following language after the statement "Open the mixing cup":

   "[redacted] (b) (4)"

6. In figure K, please explain why leftover medicine is being poured from the cup into the trash rather than in a sink.

Please respond with a re-submission of the IFU by October 30, 2013.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

KATHERINE SCHUMANN
10/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205786

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Attention: Ursula Marek, Pharm.D.
Associate Director, Global Regulatory Affairs
2015 Galloping Hill Road, K-15-3
Kenilworth, NJ 07033

Dear Dr. Marek:

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Isentress (raltegravir) (b) (4) suspension,100 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response by October 21, 2013, in order to continue our evaluation of your NDA.

1. Section 3.3.P.3.3 proposes the following range for (b) (4) Either: (a) provide data to justify the proposed ranges at commercial scale or (b) revise the commercial scale values to the set point indicated in P.2.3.8.

2. (b) (4)

3. (b) (4)

4. During the commercial (b) (4) Once data from a

statistically relevant number of commercial scale batches show no [redacted] (b) (4) potential, you may revert to USP<905> testing.

5. Provide data to support raltegravir [redacted] (b) (4) form remains unchanged during drug product manufacture and shelf-life.

6. We acknowledge the in-use stability in amendment dated 8/28/2013. Please also include information on the adequacy of [redacted] (b) (4) for batches on stability.

7. Reference is made to your amendment dated 10/1/2013. [redacted] (b) (4) We recommend the solubility test to be conducted with your proposed product once reconstituted after [redacted] (b) (4) and a minimum of [redacted] (b) (4) units per test. Collect and provide the solubility data for the registration batches.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

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

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/s/

RAPTI D MADURAWE
10/11/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**

Drug: **Isentress (raltegravir) (b) (4) suspension**

Date: **October 2, 2013**

To: **Ursula Marek, Pharm.D., Associate Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 - Comments regarding container label**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) suspension.

The review team has the following comments regarding the proposed container label for Isentress (raltegravir) (b) (4) suspension.

1. Remove the (b) (4) from the principal display panel (PDP) to avoid overcrowding and place them at the top of the back of the packet.

2. Add the statement "See back panel for opening instructions." to the PDP.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

KATHERINE SCHUMANN
10/02/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**

Drug: **Isentress (raltegravir) (b) (4) suspension**

Date: **September 24, 2013**

To: **Ursula Marek, Pharm.D., Associate Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 - Request for Information**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir (b) (4)) (b) (4) suspension.

The review team has the following request for information:

> Based on your proposed labeling and IFU, patients weighing under (b) (4) would only use a portion of what they have mixed and are instructed to discard the remaining suspension. The Division is wondering what risks are involved if patients were to save the 'left over' suspension and use it for their evening dose. Please provide a response, with consideration given to stability, palatability and safety (including the potential for microbial growth).

Please submit your response to the NDA by October 8, 2013.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

KATHERINE SCHUMANN
09/24/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir potassium) (b) (4) suspension**
Isentress (raltegravir potassium) tablets
Isentress (raltegravir potassium) chewable tablets

Date: **August 29, 2013**

To: **Ursula Marek, Pharm.D., Associate Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 - Clinical Request for Information**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir (b) (4)) (b) (4) suspension. We also refer to your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir (b) (4)) tablets and chewable tablets.

The review team has the following request for clinical information:

1. Cohort IV/V
   Subject ID 8501806. Please provide additional details with regards to the adverse event "Allergic dermatitis". Specifically, what is the allergic response to? Where is the rash located and how long did it last? Was there treatment provided for the event? If the rash was generalized, please provide additional detail as to why it is not considered treatment related.

2. Cohorts I-III
   We note that you have submitted longer-term safety data for these cohorts. However, no new labeling language has been proposed to update the safety information of raltegravir when administered to pediatric patients 2 to less than 18 years old. Please populate the table below with the requested additional information:

- Number of subjects with drug (RAL) related adverse events
- Number of subjects with adverse events leading to discontinuation and/or deaths.
- Number of subjects with SAE or Grade 3/4 clinical events
- Any new clinically significant AEs not previously observed

Week 24 - 48	Preferred terms				
	Drug related AEs	Drug related AE leading to Discontinuation	Any new AE or clinically significance not previously reported	Deaths/SAE	Grade 3 or 4 clinical AEs
Subject ID					

Post Week 48	Preferred terms				
	Drug related AEs	Drug related AE leading to Discontinuation	Any new AE or clinically significance not previously reported	Deaths/SAE	Grade 3 or 4 clinical AEs
Subject ID					

Please include the subject ID and time of event (W24-48, post W48). When available, for SAE and AEs leading to discontinuation, please include narratives, medical officer/site assessment of drug relatedness, outcome of event and action taken. In addition, please provide narratives for any adverse events coded as "drug-induced" or "drug eruption"

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

KATHERINE SCHUMANN
08/29/2013

From:	Marek, Ursula
To:	Cuff, Althea
Subject:	RE: NDA 205786 - Information Request (Correction)
Date:	Wednesday, August 14, 2013 10:55:17 AM

Thanks!

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Wednesday, August 14, 2013 10:54 AM
To: Marek, Ursula
Subject: RE: NDA 205786 - Information Request (Correction)

Hi Ursula,

I apologize but I missed sending the rest of the Information Request, please see the corrected IR.

1. The "critical in-process controls" listed in Section 3.2.P.3.4 - 1.1.1 have the potential to impact critical quality attributes. Therefore, the statement in 3.2.P.3.4 that no parameters were considered to be "critical" appear to be based on preselection of operating ranges or magnitude of product quality response. However, changes from the preselected targets/ranges (i.e. proposed Proven Acceptable Ranges) could have a minor, moderate or substantial potential to adversely affect product quality. The Agency's expectation is that the potential impact of changes to process parameters and in-process controls, including those designated as non-critical process parameters, as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.

2. Section 3.2.P.2.1 indicates the formal stability batches and the clinical batches were manufactured by the same proposed commercial manufacturing process. If not, please provide a side by side comparison (tabular format preferred) of all formulation and manufacturing process differences and include available data in support of the change.

3. Table 3 in Section 3.2.P.2.2 provides in-use stability data (assay and degradant) for reconstituted suspensions at 5, 15, and 30 min timepoints. Please include data for the 6 hr timepoint as a 30-minute patient in-use period is proposed for the oral suspension based on the 6 hr stability data. Additionally, for all test timepoints, include pH and "fineness of dispersion" data for the reconstituted suspension.

4. Section 3.2.P.8.3.3 contains in-use stability data for the reconstituted suspension. Please clarify the suspension test time point (i.e., 30 min or 6 hours?) for the data given in 3.2.P.8.3.3.

Thanks, Althea

From: Marek, Ursula [mailto:ursula.marek@merck.com]
Sent: Wednesday, August 14, 2013 10:04 AM
To: Cuff, Althea
Subject: RE: NDA 205786 - Information Request

Hi Althea,

Receipt confirmed.

Thanks!
Ursula

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Wednesday, August 14, 2013 9:50 AM
To: Marek, Ursula
Subject: NDA 205786 - Information Request

Dear Ursula,

In reference to NDA 205786, we have the following Information Request. Please respond by August 28, 2013:

The "critical in-process controls" listed in Section 3.2.P.3.4 - 1.1.1 have the potential to impact critical quality attributes. Therefore, the statement in 3.2.P.3.4 that no parameters were considered to be "critical" appear to be based on preselection of operating ranges or magnitude of product quality response. However, changes from the preselected targets/ranges (i.e. proposed Proven Acceptable Ranges) could have a minor, moderate or substantial potential to adversely affect product quality. The Agency's expectation is that the potential impact of changes to process parameters and in-process controls, including those designated as non-critical process parameters, as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.

Please confirm receipt of this e-mail.

Thanks,

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

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (One Merck Drive, Whitehouse Station, New Jersey, USA 08889), and/or its affiliates Direct contact information for affiliates is available at http://www.merck.com/contact/contacts.html) that may be confidential, proprietary copyrighted and/or legally privileged. It is intended solely for the use of the individual or entity named on this message. If you are not the intended recipient, and have received this message in error, please notify us immediately by reply e-mail and then delete it from your system.

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/s/

ALTHEA CUFF
08/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205786
NDA 22145 S-031
NDA 203045 S-009

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Merck Sharp & Dohme Corp.
Attention: Ursula Marek, Pharm.D.
Associate Director, Global Regulatory Affairs
2015 Galloping Hill Road, K-15-3
Kenilworth, NJ 07033

Dear Dr. Marek:

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Isentress (raltegravir) (b) (4) suspension, 100 mg.

Please also refer to your Supplemental New Drug Applications (sNDAs) dated June 25, 2013, received June 26, 2013, submitted under section 505(b) of the FDCA for Isentress (raltegravir) film-coated tablets, 400 mg, and Isentress (raltegravir) chewable tablets, 25 mg and 100 mg.

We also refer to your amendments dated July 11, 2013, July 18, 2013 and July 31, 2013.

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), these applications are considered filed 60 days after the date we received your applications. The review classification for these applications is **Priority**. Therefore, the user fee goal date for NDA 205786 is December 27, 2013. The user fee goal date for NDA 22145 S-031 and NDA 203045 S-009 is December 26, 2013.

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

205786 by December 6, 2013. We plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests for NDA 22145 S-031 and NDA 203045 S-009 by December 5, 2013.

During our filing review of your applications, we identified the following potential review issues:

1. The dosage form of your proposed product, [redacted] (b) (4) suspension, requires dissolution testing. However, you claim that your proposed product, once reconstituted, is NOT a suspension, [redacted] (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the applications and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the applications. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your applications.

We request that you submit the following information:

1. Please refer to our clinical pharmacology information request of August 6, 2013 requesting additional data in support of your population PK report for raltegravir [redacted] (b) (4) suspension.

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.

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 (as applicable). 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) 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 acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 4 weeks to 2 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

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

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/s/

JEFFREY S MURRAY
08/14/2013

From: Cuff, Althea
To: Marek, Ursula (ursula.marek@merck.com)
Subject: NDA 205786 - Information Request
Date: Wednesday, August 14, 2013 9:49:00 AM

Dear Ursula,

In reference to NDA 205786, we have the following Information Request. Please respond by August 28, 2013:

The "critical in-process controls" listed in Section 3.2.P.3.4 - 1.1.1 have the potential to impact critical quality attributes. Therefore, the statement in 3.2.P.3.4 that no parameters were considered to be "critical" appear to be based on preselection of operating ranges or magnitude of product quality response. However, changes from the preselected targets/ranges (i.e. proposed Proven Acceptable Ranges) could have a minor, moderate or substantial potential to adversely affect product quality. The Agency's expectation is that the potential impact of changes to process parameters and in-process controls, including those designated as non-critical process parameters, as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.

Please confirm receipt of this e-mail.

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
08/14/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir) (b) (4) suspension**
Isentress (raltegravir) tablets
Isentress (raltegravir) chewable tablets

Date: **August 13, 2013**

To: **Ursula Marek, Pharm.D., Associate Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

From: **Stacey Min, PharmD, Regulatory Project Manager, DAVP, on behalf of Katherine Schumann, M.S., Regulatory Project Manager, DAVP**

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 – Initial Comments Regarding Instructions for Use**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir) (b) (4) suspension. We also refer to your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir) tablets and chewable tablets.

After a preliminary review of the new Instructions for Use (IFU) document, DAVP and the Patient Labeling team in the Division of Medical Policy Programs (DMPP) have the following initial comments. Please note that additional comments on the IFU will be conveyed during the review cycle, pending full review of the patient labeling.

1. The IFU is provided as a Word document; however, it is in a graphic format that does not allow the Patient Labeling Team to edit the document. The PLT reviewer conveyed this to Katherine Schumann on 8/1/13 and Katherine sent an information request (IR) to the Applicant requesting the document in a format that can be edited.
2. The Applicant should clarify whether the mixing cup lids are attached by a hinge and if so, that they snap into place. The mixing cups appear to have rims that make it unclear whether the lids snap on, or are closed by twisting to seal the mixing cup.

3. Enlarge all figures and clearly demonstrate a person doing each action.
4. All figures should be labeled sequentially Figure A, Figure B, etc. and referenced in the adjacent text, beginning with the figure at the beginning of the IFU showing supplies provided in the kit.
5. Revise the figure referenced above or add an additional figure that shows the syringe with the parts (barrel, plunger, and tip) and markings clearly labeled. Also, please remove the brackets around the supplies in the figure.
6. Steps should be sequentially labeled with numerals (ie: Step 1, Step 2, Step 3, Step 4).
7. Figure 1 implies that the water is [redacted] (b) (4). It is more intuitive to show water being used from a faucet. Revise the figure to show a sink and faucet, and the cup being filled with the water.
8. Figure 3 may be confusing for patients. Revise the figure to show the remaining water being poured into the drain in a sink.
9. Figure 7 appears to show the cup being turned from side-to-side. Clarify whether to actually shake the cup up and down for example, and if so, revise the figure so that the action shown aligns better with the information in the text.
10. Figure 10 does not clearly represent disposal into a trash can. Revise the figure so that the patient can identify the trash can, and someone pouring the leftover medicine into the trash can. The action shown in the figure should be better aligned with the direction given in the text.
11. In Figure 11 the faucet gives the appearance that it is suspended in air. Revise accordingly.

Please respond with a re-submission of the IFU by September 6, 2013.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

STACEY MIN
08/13/2013

From: Schumann, Katherine
To: "Marek, Ursula"
Subject: RE: NDA 205786 - Request for Information
Date: Friday, August 09, 2013 8:57:00 AM

Ursula,

Thank you for the update below. I have consulted with DMEPA, and they would like the blank physical samples now. Please include everything that is available now, including the mixing cups and syringes, if possible.

DMEPA will also need to see the final samples as soon as they are available.

Please let me know if you have any questions.

Warm Regards,
Katie

From: Marek, Ursula [mailto:ursula.marek@merck.com]
Sent: Thursday, August 08, 2013 11:33 AM
To: Schumann, Katherine
Subject: RE: NDA 205786 - Request for Information

Hi Katie,

Regarding the request for the physical samples of the carton and packets for the granules of suspension, unfortunately we will not be able to send the final samples of the carton and foil pouch until the middle of October as there is a lead time for printing on the foil pouches. However, we can provide a blank copy of the foil pouch and carton without the printed artwork in the meantime if it would be helpful (please note a pdf version of the printed artwork for the carton and pouch was submitted with the NDA). Please let me know if you would like me to send you the blank copies.

Thanks,
Ursula

From: Schumann, Katherine [mailto:Katherine.Schumann@fda.hhs.gov]
Sent: Thursday, July 25, 2013 3:55 PM
To: Marek, Ursula
Subject: NDA 205786 - Request for Information

Dear Ursula,

Please find attached the request from our eData group in the Office of Business Informatics, as well as additional requests from the clinical team (for the coding dictionary) and DMEPA (for the samples). I have also requested an MS Word version of the Instructions for Use, as I know we generally need this for review.

If you have any questions, or you think that the requested timeframe for responding will not be

feasible, please let me know.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

From: Marek, Ursula [mailto:ursula.marek@merck.com]
Sent: Thursday, July 25, 2013 3:18 PM
To: Schumann, Katherine; Borbor, Mammah
Cc: Chambers, Thomas
Subject: Isentress- Coverage for July 29-Aug 2nd

Hello,

I wanted to let you know that I will be on vacation next week. Below please find the contact information for my back-up during this time. I would appreciate it if you could contact Thomas Chambers for any issues related to Isentress and copy me.

Thomas Chambers
Email: thomas_chambers2@merck.com
Phone: (267) 305-6722

Thank you,
Ursula

Ursula Marek, Pharm.D.
Global Regulatory Affairs
Merck & Co., Inc
2015 Galloping Hill Rd.
K-15-3, MS 3175
Kenilworth, NJ 07033-0530
(P): 908-740-3359
(F): 908-740-2143
Ursula.marek@merck.com

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/s/

KATHERINE SCHUMANN
08/09/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**

Drug: **Isentress (raltegravir potassium) (b) (4) suspension**

Date: **August 6, 2013**

To: **Ursula Marek, Pharm.D., Associate Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 - Request for Information**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir (b) (4)) (b) (4) suspension.

After a preliminary review of your application, the clinical pharmacology team has the following request for information:

> Please submit all raw data, derived data sets, codes (NONMEM, SPlus, R, etc) that were used to conduct modeling and simulation, generate tables and graphs in the report "Population PK modeling analysis report to support the pediatric filing of raltegravir (MK-0518) granules for suspension formulation in HIV infected pediatric patients 4 weeks to less than 2 years of age."

Please submit your response within 10 days of receipt of this request.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

KATHERINE SCHUMANN
08/06/2013

From:	Schumann, Katherine
To:	ursula.marek@merck.com
Cc:	thomas_chambers2@merck.com
Subject:	NDA 205786 - Request for Instructions for Use
Date:	Thursday, August 01, 2013 11:08:00 AM

Ursula,

Our patient labeling team has requested that you re-submit the Instructions for Use document for the Isentress (b) (4) suspension in a format that allows them to edit the text. Although we received the Word document submitted on July 11, 2013, because the information was provided as an image, we are not able to manipulate the text.

Please submit this to the NDA at your earliest convenience, no later than August 26, 2013.

Warm Regards,
Katie

Katherine Schumann, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6360
Silver Spring, MD 20993-0002
Phone: (301) 796-1182
Fax: (301) 796-9883
Email: Katherine.Schumann@fda.hhs.gov

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/s/

KATHERINE SCHUMANN
08/01/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

MEMORANDUM OF ELECTRONIC CORRESPONDENCE

NDA: **205786**
22145 S-031
203045 S-009

Drug: **Isentress (raltegravir potassium) (b) (4) suspension**
Isentress (raltegravir potassium) tablets
Isentress (raltegravir potassium) chewable tablets

Date: **July 25, 2013**

To: **Ursula Marek, Pharm.D., Associate Director, Global Regulatory Affairs**

Sponsor: **Merck Sharp & Dohme Corp.**

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

Subject: **NDA 205786 / NDA 22145 S-031 / NDA 203045 S-009 - Request for Information**

Please refer to your New Drug Application (NDA) dated June 26, 2013, received June 27, 2013 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Isentress (raltegravir (b) (4)) (b) (4) suspension. We also refer to your supplemental NDAs dated June 25, 2013, received June 26, 2013 for Isentress (raltegravir (b) (4)) tablets and chewable tablets.

After a preliminary review of your applications, we have the following requests:

1. Please re-submit the proposed Instructions for Use document in MS Word format, in addition to the PDF document already submitted, in order to facilitate our review.

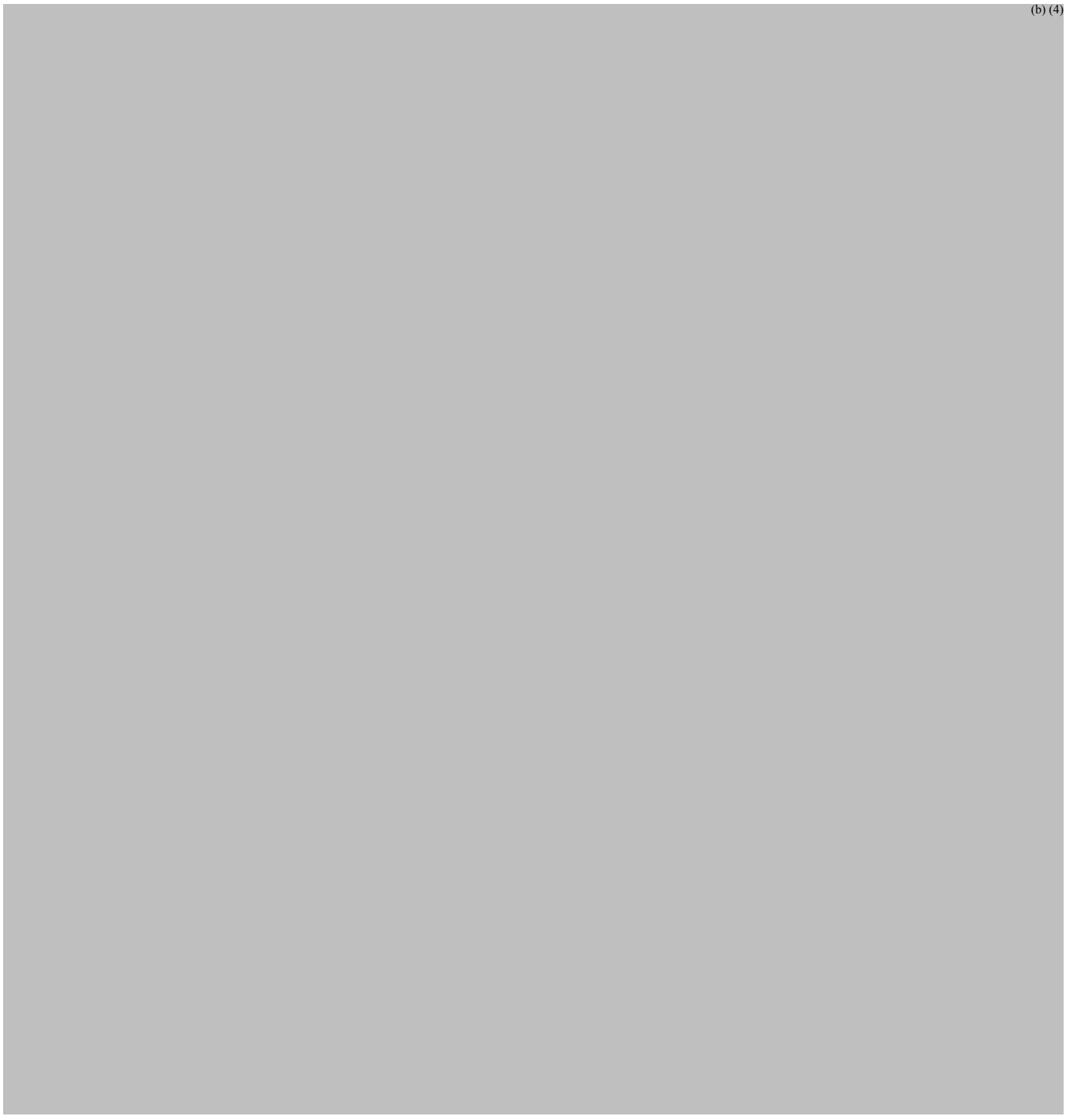
2. Please submit physical samples of the carton and packets for the (b) (4) suspension. Three samples of each is preferred.

3. Please submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It may be is submitted as a PDF document, but it should be submitted in both directions (verbatim → preferred and preferred → verbatim).

4. The Office of Business Informatics has reviewed your submission and requests that you correct your application as indicated below.

   The Agency prefers the sponsor follow the Study Data Specifications guidance for datasets submission; including the structure of the directories (folders) within the submission layout. Submissions of datasets that do not follow the guidance can be problematic to the Agency's review processes.

(b) (4)



Please submit your response to these requests by August 19, 2013.

Please respond via email (Katherine.Schumann@fda.hhs.gov) to confirm receipt. We are providing the above information via electronic mail for your convenience. Please contact me at (301) 796-1182 if you have any questions regarding the contents of this transmission.

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

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/s/

KATHERINE SCHUMANN
07/25/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205786

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Ursula Marek, Pharm.D.
Associate Director, Global Regulatory Affairs
2015 Galloping Hill Road, K-15-3
Kenilworth, NJ 07033

Dear Dr. Marek:

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

Name of Drug Product: Isentress® (raltegravir (b) (4)) (b) (4) for suspension, 100 mg

Date of Application: June 26, 2013

Date of Receipt: June 27, 2013

Our Reference Number: NDA 205786

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 26, 2013, 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 me at (301) 796-1182 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

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

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KATHERINE SCHUMANN
07/09/2013