

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205786Orig1s000**

**OTHER REVIEW(S)**

**Division of Antiviral Products**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:**

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

**Name of Drug:**

ISENTRESS<sup>®</sup> (raltegravir) for oral suspension  
ISENTRESS<sup>®</sup> (raltegravir) film-coated tablets  
ISENTRESS<sup>®</sup> (raltegravir) chewable tablets

**Applicant:**

Merck Sharp & Dohme Corp.

**Labeling Reviewed**

**Submission Date:** December 19, 2013

**Receipt Date:** December 19, 2013

**Background and Summary Description:**

Merck submitted NDA 205786 for ISENTRESS (raltegravir) for oral suspension to expand the patient population to include pediatric patients ages 4 weeks and older. ISENTRESS (raltegravir) chewable tablets were previously approved under original NDA 203045 for pediatric patients down to 2 years of age. Companion efficacy supplements were also submitted to NDA 22145 (S-031) for raltegravir tablets and NDA 203045 (S-009) for raltegravir chewable tablets, as all three NDAs share labeling. The new NDA was submitted in response to PREA PMC 582-3 established with the accelerated approval of NDA 22145 dated October 12, 2007.

The submission included new carton and container labels for the oral suspension, as well as a new Instructions for Use document that is proposed as part of the patient labeling. This review addresses the Prescribing Information, Patient Prescribing Information and Instructions for Use.

On Wednesday, December 18, CMC Team Lead Steve Miller provided specific recommendations for how the Applicant should reference the oral suspension dosage form throughout the label to improve readability. (b) (4)

(b) (4)

(b) (4)

The final draft of the labeling (sponsor's version submitted December 19, 2013) is being compared to the last approved labeling dated October 24, 2013 (NDA 22145 S-030 / NDA 203045 S-008). In the review below, new text is indicated in **blue** font, deleted text is indicated in strikethrough.

## Review

### GENERAL

Throughout the labeling, minor editorial changes were made, such as changes in punctuation. As a new Table 2 was added to the Dosage and Administration section of the PI, all subsequent table numbers were shifted.

### HIGHLIGHTS

The new dosage form was added to the product title section:

**ISENTRESS<sup>®</sup> (raltegravir) film-coated tablets, for oral use**  
**ISENTRESS<sup>®</sup> (raltegravir) chewable tablets, for oral use**  
**ISENTRESS<sup>®</sup> (raltegravir) for oral suspension**

(b) (4)

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## Recommendations

It will be conveyed to the applicant that labeling is acceptable, and an approval letter should be sent. Please refer to the clinical, clinical pharmacology, CMC, biopharmaceutics and clinical virology reviews and addenda for additional information.

<u>Katherine Schumann</u>	<u>December 20, 2013</u>
Regulatory Project Manager	Date
<u>Elizabeth Thompson</u>	<u>December 20, 2013</u>
Chief, Project Management Staff	Date

41 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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KATHERINE SCHUMANN  
12/20/2013

ELIZABETH G THOMPSON  
12/20/2013

## **SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies**

<b>Product Title<sup>1</sup></b>	<b>ISENTRESS<sup>®</sup> (raltegravir) film-coated tablets, for oral use ISENTRESS<sup>®</sup> (raltegravir) chewable tablets, for oral use ISENTRESS<sup>®</sup> (raltegravir) <sup>(b) (4)</sup> suspension, <sup>(b) (4)</sup></b>
Applicant	<b>Merck Sharp &amp; Dohme Corp., a subsidiary of Merck &amp; Co., Inc.</b>
Application/Supplement Number	NDA 205785, 22145 S-031, 203045 S-0009
Type of Application	Original, Efficacy Supplement, Efficacy Supplement
Indication(s)	In combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks of age and older
Office/Division	OAP/DAVP
Division Project Manager	Katie Schumann
Date FDA Received Application	June 26, 2013
Goal Date	December 26, 2013
Date PI Received by SEALD	December 10, 2013
SEALD Review Date	December 12, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

<sup>1</sup> Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

# Selected Requirements of Prescribing Information

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:** *According to the RPM, a waiver has been previously granted by the review division.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

## Selected Requirements of Prescribing Information

***Comment:*** Prescribers should be directed to the most specific numerical identifier; in I&U, prescribers are directed to "14" where specific subsections may be more appropriate. In DI, the first bullet directs prescribers to "7" where "7.1, 7.2" may be more appropriate..

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

***Comment:***

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

***Comment:***

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

***Comment:***

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

***Comment:***

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

***Comment:***

## Selected Requirements of Prescribing Information

### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.
- Comment:
- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
- Comment:
- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.
- Comment:
- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).
- Comment:

### Recent Major Changes (RMC) in Highlights

- YES** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.
- Comment:
- NO** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.
- Comment: *The date is missing; this should likely state: 12/2013. Also, subsection headings and numbers are missing from the D&A RMC. Consider: Dosage and Administration, General Dosing Recommendations (2.1) 12/2013 and on the following line Dosage and Administration, Pediatrics (2.3) 12/2013.*
- YES** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
- Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.
- Comment:

### Dosage Forms and Strengths in Highlights

## Selected Requirements of Prescribing Information

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

### Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The date is missing and should read: 12/2013*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:***

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

## Selected Requirements of Prescribing Information

**Comment:** *The format for cross-references is correct, however, the prescriber should be directed to the most specific numerical identifier. In I&U, Section "14" is cross-referenced, where specific subsections may be more appropriate, subsection 2.1 has a cross-reference to "7" where "7.2" may be more appropriate, subsection 7.2 cross-references "2" where "2.1" may be more appropriate and in subsection 12.3, section "7" is cross-referenced where "7.2" may be more appropriate.*

- YES** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

**Comment:**

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

**Comment:**

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

**Comment:**

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

**Comment:**

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:** *Best Practice would be to just have two subsections, 6.1 Clinical Trials Experience and 6.2 Postmarketing Experience; the current subsections related to clinical trials experience would be under 6.1 and identified with subheadings only. The required statement would then be placed immediately after the subsection heading 6.1 Clinical Trials Experience. When information is "floating" (between section heading 6 and subsection heading 6.1), as it is currently, prescribers who access the information electronically may miss this statement as it is not picked up in a hyperlink.*

## Selected Requirements of Prescribing Information

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:**

### **PATIENT COUNSELING INFORMATION Section in the FPI**

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

- [text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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/s/  
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ELIZABETH A DONOHOE  
12/12/2013

ERIC R BRODSKY  
12/12/2013

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

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

**Memorandum**

**Date:** November 22, 2013

**To:** Katherine Schumann, MS, Regulatory Project Manager  
Division of Antiviral Products

**From:** Jessica Fox, PharmD, Regulatory Review Officer  
Office of Prescription Drug Promotion

**Subject:** NDA 022145/S-031  
ISENTRESS (raltegravir) film-coated tablets, for oral use

NDA 203045/S-009  
ISENTRESS (raltegravir) chewable tablets, for oral use

NDA 205786  
ISENTRESS (raltegravir) (b) (4) suspension, (b) (4)

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As requested in the Division of Antiviral Products' (DAVP) consult dated July 16, 2013, the Office of Prescription Drug Promotion (OPDP) has reviewed the ISENTRESS prescribing information, carton/container labeling, patient package insert, and instructions for use.

OPDP has reviewed the proposed substantially complete version of the prescribing information obtained via the DAVP eRoom on November 22, 2013, and has the following comment:

- The INDICATIONS AND USAGE section of the Highlights omits important information that is presented in the INDICATIONS AND USAGE section of the Full Prescribing Information. Specifically, it omits the underlined information:

ISENTRESS® is [REDACTED] (b) (4)  
[REDACTED] (HIV-1)  
infection in patients 4 weeks of age and older.

- The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response [see Clinical Studies (14)].

We strongly recommend including this information in the INDICATIONS AND USAGE section of the Highlights.

OPDP has reviewed the carton/container labeling submitted by the sponsor on June 27, 2013, accessed via EDR Location: <\\CDSESUB1\evsprod\NDA205786\205786.enx>, and has the following comment:

- The carton/container labeling include the statement, “For Pediatric Patients 4 weeks [REDACTED] (b) (4) This statement is not consistent with the DOSAGE AND ADMINISTRATION section of the Full Prescribing Information, which states, “Patients can remain on the [REDACTED] (b) (4) suspension formulation as long as their weight is below 20 kg.” We recommend revising the carton/container labeling for consistency with the prescribing information.

The Division of Medical Policy Programs and OPDP have provided a single, consolidated review of the patient package insert and instructions for use entered into DARRTS on November 22, 2013.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Jessica Fox at (301) 796-5329 or at [Jessica.Fox@fda.hhs.gov](mailto:Jessica.Fox@fda.hhs.gov).

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/s/

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JESSICA M FOX  
11/22/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: November 22, 2013

To: Debra Birnkrant, MD  
Director  
**Division of Antiviral Products (DAVP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Jessica M. Fox, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and  
Instructions for Use (IFU)

Drug Name (established name), Dosage Form and Route, Application Number, Supplement Number: ISENTRESS (raltegravir ) (b) (4) suspension, (b) (4) NDA 205-786  
ISENTRESS (raltegravir ) film-coated tablets, for oral use  
NDA 22-145/S-031  
ISENTRESS (raltegravir ) chewable tablets, for oral use,  
NDA 203-045/S-009

Applicant: Merck Sharp and Dohme Corp.

## 1 INTRODUCTION

On August 18, 2006, the Agency issued a Written Request for pediatric studies of ISENTRESS (raltegravir) film-coated tablets, New Drug Application (NDA) 22-145. The Written request was amended at the time of the original approval of NDA 22-145 on June 27, 2007 (study commitment #3), and the final Written Request was issued on October 19, 2010.

On June 27, 2013 Merck Sharp and Dohme Corp. submitted for the Agency's review original NDA 205-786 for ISENTRESS (raltegravir) (b)(4) suspension, and provided a pediatric study report (IMPACCT P1066/Merck PN022), in order to fulfill their pediatric postmarketing commitment. ISENTRESS (raltegravir) is currently indicated in combination with other antiretroviral agents for the treatment of HIV-1infection. The Applicant proposes to expand the indication for ISENTRESS to include the use of (b)(4) suspension to treat pediatric patients ages 4 weeks (b)(4).

On June 26, 2013, the Applicant simultaneously submitted for the Agency's review, Prior Approval Supplements (Efficacy) to their approved NDA 22-145/S-031 for ISENTRESS (raltegravir) film-coated tablets (originally approved October 12, 2007), and NDA 203-045/S-009 ISENTRESS (raltegravir) chewable tablets (originally approved December 21, 2011), including proposed labeling to expand the indication for ISENTRESS to include use of the (b)(4) suspension to treat pediatric patients ages 4 weeks (b)(4).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on July 16, 2013, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ISENTRESS (raltegravir) film-coated tablets, chewable tablets, and (b)(4) suspension, and Instructions for Use (IFU) for ISENTRESS (raltegravir) (b)(4) suspension.

## 2 MATERIAL REVIEWED

- Draft ISENTRESS (raltegravir) film-coated tablets, chewable tablets PPI and (b)(4) suspension PPI, received on June 26, 2013 and June 27, 2013, revised throughout the review cycle, and received by DMPP and OPDP on November 8, 2013.
- Draft ISENTRESS (raltegravir) (b)(4) suspension IFU received on June 27, 2013, revised by the Applicant throughout the review cycle, and received by DMPP and OPDP on November 8, 2013.
- Draft ISENTRESS (raltegravir) film-coated tablets, chewable tablets, and (b)(4) suspension Prescribing Information (PI) received on June 26, 2013 and June 27, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2013.

- Approved TIVICAY(dolutegravir) tablets labeling dated August 12, 2013

### **3 REVIEW METHODS**

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the IFU the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our collaborative review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.
- The appended IFU incorporates DMPP and DMEPA comments.

### **4 CONCLUSIONS**

The PPI and IFU are acceptable with our recommended changes.

### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

30 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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SHARON R MILLS  
11/22/2013

JESSICA M FOX  
11/22/2013

BARBARA A FULLER  
11/22/2013

LASHAWN M GRIFFITHS  
11/22/2013

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: November 13, 2013

TO: Debra B. Birnkrant, M.D.  
Director, Division of Antiviral Products  
Office of Antimicrobial Products

FROM: Xikui Chen, Ph.D.  
Pharmacologist, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations  
and  
William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 205-786 (raltegravir  
(b)(4)suspension), NDA 22-145/S-031  
(raltegravir tablets), and NDA 203-045 (raltegravir  
chewable tablets), Sponsored by Merck Sharp & Dohme  
Corp.

At the request of the Division of Antiviral Products, the Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspections of the following study:

**Study Number:** IMPAACT P1066 (Merck Protocol 022)  
**Study Title:** "A Phase I/II, multicenter, open-label, noncomparative study of the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) group to evaluate the safety, tolerability, pharmacokinetics, and antiretroviral activity of raltegravir (Isentress, MK-0518) in HIV-1 infected children and adolescents"

The audit included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firms' management and staff.

**Clinical Sites:**

The inspections of the study's clinical portions were conducted by ORA Investigator Carmen Fisher of KAN-DO at the University of KwaZulu Natal, Nelson R. Mandela School of Medicine, Durban, South Africa (October 14-17, 2013), and the Shandukani Research Wits Reproductive Health & HIV Institute (WRHI), Johannesburg, South Africa (October 21-25, 2013). RNA processing was conducted in clinical pathology laboratories at WRHI, and LCDR Fisher confirmed that there were no transcription errors in reporting the WRHI RNA test results to the NDA report.

Following the inspections, LCDR Fisher did not issue Form FDA-483 at either of the two clinical sites.

**Bioanalytical Site:**

(b)(4)  
(b)(4)  
(b)(4) Following the  
(b)(4) inspection (b)(4), Ms. (b)(4) and Dr. (b)(4) issued Form FDA-483 (**Attachment 1**). The Form FDA-483 observation and my evaluations follow:

1. For study IMPAACT P1066, failure to employ standard quality control techniques to Cohorts IV and V. Specifically, your firm failed to record, for 12 out of 35 analytical runs, including but not limited to, calibration standards, quality control samples, internal standard, and identification of the samples on the Daily Assay Worksheet.

The Daily Assay Worksheet was not completed for 12 out of 35 analytical runs: 120302, 120305, 120322, 120406, 120409, 120423, 120822, 120927, 121016, 130115, 130130, and 130213. Preparations of calibration standards, internal standard, and quality control samples were recorded in preparation sheets; however, the preparations were not linked to these particular analytical runs. During the inspection, (b)(4) personnel said that they will record complete information on Daily assay Worksheet in the future.

Page 3 - NDA 205-786 (raltegravir (b)(4) suspension), NDA 22-145/S-031 (raltegravir tablets), and NDA 203-045 (raltegravir chewable tablets)

As of this writing, OSI has not received the firm's response to the Form FDA-483 observation. If we receive a significant response, we will amend this review.

In my opinion, responses from (b)(4) are unlikely to impact the raltegravir assay results or my recommendation to accept the data for review.

We note that pharmacokinetic interpretations relied on assays of liquid plasma samples. However, parallel assays at (b)(4) with dried blood spot (DBS) samples yielded results comparable to the plasma samples.

**Conclusion:**

Following the above inspections, I recommend that the clinical and bioanalytical data from study IMPAACT P1066 are acceptable for review.

Xikui Chen, Ph.D.  
Pharmacologist

Page 4 - NDA 205-786 (raltegravir [REDACTED] suspension), NDA 22-145/S-031 (raltegravir tablets), and NDA 203-045 (raltegravir chewable tablets)

**Final Classifications:**

**NAI - University of KwaZulu Natal, Nelson R Mandela School of Medicine, Durban, South Africa  
FEI 3010440309**

**NAI - Shandukani Research Wits Reproductive Health & HIV Institute (WRHI), Johannesburg, South Africa  
FEI 3010440310**

**VAI -**

[REDACTED] (b) (4)

CC:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Skelly/Dejernett/Chen/CF

OSI/DBGLPC/Choi/Bonapace/Mada/Ayala

OND/OAP/DAVP/Birnkrant/Schumann

OTS/OCP/DCP/Lazor/Booth

ORA/NOL-DO/Staples

ORA/KAN-DO/Fisher

Draft: XC 11/6/2013

Edit: MFS 11/6/2013; SHH 11/6/2013; WHT 11/6/2013; 11/13/13

OSI: BE File 6484

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ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/ Inspections/BE Program/Clinical Sites/University of KwaZulu Natal, Durban, South Africa

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/ Inspections/BE Program/Clinical Sites/Shandukani Research Wits Reproductive Health & HIV Institute, Johannesburg, South Africa

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/ Inspections/BE

Program/Analytical Sites/ [REDACTED] (b) (4)

[REDACTED] (b) (4)

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/s/  
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XIKUI CHEN  
11/13/2013

SAM H HAIDAR  
11/14/2013

WILLIAM H TAYLOR  
11/14/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: September 30, 2013

Reviewer: Morgan Walker, PharmD, MBA  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Isentress (Raltegravir) (b)(4) Suspension  
100 mg

Application Type/Number: NDA 205786

Applicant/sponsor: Merck and Co.

OSE RCM #: 2013-1651

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## Contents

1	INTRODUCTION .....	1
1.1	Background .....	1
1.2	Regulatory History .....	1
1.3	Product Information.....	1
2	METHODS AND MATERIALS REVIEWED .....	1
2.1	Selection of Medication Error Cases .....	2
2.2	Labels and Labeling .....	2
2.3	Previously Completed Reviews.....	3
3	MEDICATION ERROR RISK ASSESSMENT .....	3
3.1	Medication Error Cases .....	3
3.2	Proposed Insert Labeling, Patient Package Insert, and Instructions for Use Risk Assessment.....	3
3.3	Integrated Summary of Medication Error Risk Assessment .....	5
4	CONCLUSIONS and RECOMMENDATIONS.....	6
	Appendices.....	7

## 1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling, and instructions for use for Isentress (Raltegravir) (b)(4) Suspension, 100 mg NDA 205786 for areas of vulnerability that could lead to medication errors.

### 1.1 BACKGROUND

The Applicant submitted NDA 205786 on June 26, 2013 for Isentress (Raltegravir) (b)(4) suspension for pediatric patients aged 4 weeks (b)(4). Isentress is currently marketed as 400 mg film-coated tablets (NDA 22145/S-031), 100 mg and 25 mg chewable tablets (NDA 20345/S-009). The Applicant plans to have the proposed and currently marketed products share one insert labeling.

### 1.2 REGULATORY HISTORY

Isentress film-coated tablet, 400 mg (NDA 22145/S-031) was approved on October 12, 2007. Isentress chewable tablets, 100 mg and 25 mg (NDA 20345/S-009) were approved on December 21, 2011.

### 1.3 PRODUCT INFORMATION

The following proposed product information is provided in the June 26, 2013 submission.

- Active Ingredient: Raltegravir
- Indication of Use: For use in combination with other antiretroviral agents for the treatment of HIV-1 infection.
- Route of Administration: Oral
- Dosage Form: (b)(4) suspension
- Strength: 100 mg
- Dose and Frequency: The dosing is weight based, twice daily. The weight-based dosing recommendation for (b)(4) suspension is based on approximately 6 mg/kg/dose twice daily.
- How Supplied: Child-resistant single-use foil packets, packaged as a kit with two 5 mL dosing syringes and two mixing cups.
- Storage: 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature. Store in the original container. Do not open foil packet until ready for use.

## 2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Isentress medication error reports (See Appendix A for a description of the FAERS database). We also reviewed the Isentress labels, package insert labeling, and instructions for use submitted by the Applicant.

## 2.1 SELECTION OF MEDICATION ERROR CASES

We searched FAERS using the strategy listed in Table 1.

<b>Table 1: FAERS Search Strategy</b>	
Date	July 11, 2013
Drug Names	Raltegravir (active ingredient) Isentress (trade name)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The FAERS database search identified 62 cases. Each case was reviewed for relevancy and duplication. After individual review, 40 cases were not included in the final analysis for the following reasons:

- Accidental overdose (n=2)
- Adverse drug reactions unrelated to medication error (n=6)
- Dose omission (n=9)
- Duplicate cases (n=2)
- Expired drug use (n=1)
- Intentional overdoses (n=7)
- Medication errors unrelated to Isentress (n=6)
- No medication error reported (n=6)
- Prescribing error which did not state any details regarding the actual error (n=1)

## 2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 26, 2013 (Appendix B)
- Carton Labeling submitted June 26, 2013 (Appendix C)
- Insert Labeling submitted June 26, 2013
- Patient Packaging Insert submitted June 26, 2013
- Instructions For Use submitted June 26, 2013

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### 2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously completed a proprietary name, label and labeling review for Isentress film-coated tablet in OSE Review # 2007-962 on March 26, 2007 and a 915 review in OSE Review # 2009-482. We also completed a label and labeling review for Isentress chewable tablets in OSE Review # 2011-2520 on Nov 15, 2011. Thus, we reviewed them to ensure all of our recommendations were considered or implemented. We also reviewed our previous reviews for any issues that may be relevant to this review. Our evaluation found that all of our recommendations were implemented.

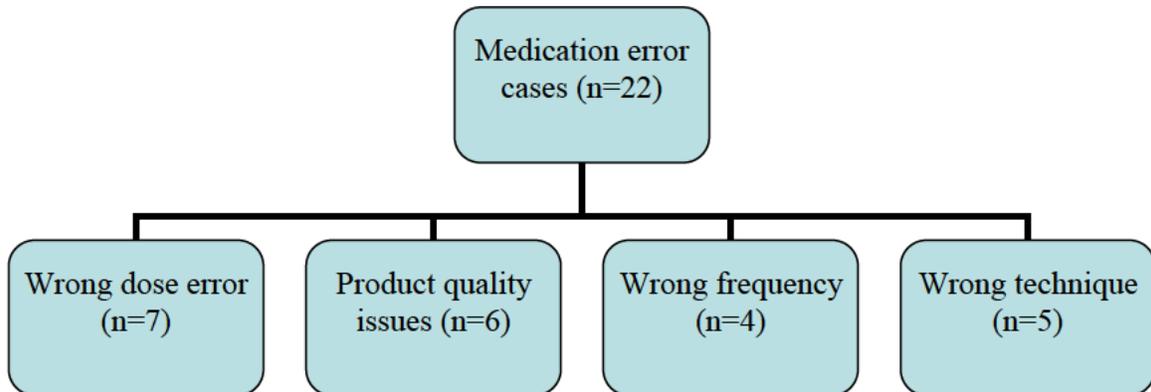
## 3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of the proposed Isentress labels and labeling.

### 3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, 22 Isentress medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter<sup>2</sup>. Figure 1 provides a stratification of the number of cases included in the review by type of error.

**Figure 1: Isentress medication errors (n = 22) categorized by type of error**



#### **Wrong Dose Errors**

##### Overdose Errors

Case number 6638849 v 1 reported a patient's prescriptions were misfilled and the patient ended up taking twice as much Isentress and half as much Prezista. No outcomes reported.

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<sup>2</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Case number 7191356 v1 reported a patient who took Isentress 3 times a day instead of 2 times a day. No cause reported. Patient outcomes reported were flushing.

Case number 8083371 v 2 reported a subject who was enrolled in the Merck study that was taking two tablets of Isentress in the morning and 2 tablets in the evening. No cause reported. Patient was reported to be asymptomatic after this error occurred.

Case number 8174355 v2 reported a subject who was enrolled in an open-label ViiV supported study that experienced an asymptomatic overdose. No cause reported.

Case number 8781547 v1 reported a patient who experienced an overdose of Isentress. No cause or patient outcomes reported.

Case number 9105124 v1 reported a patient, from an unknown date, was taking a daily totally dose of 1200 milligrams of Isentress. No cause or patient outcomes reported.

#### Under-dose Errors

Case number 9382066 v1 reported a physician who performed prescribed underdoses when the condition of the patients improved while on Isentress, the physician dosed patients 1 tablet once daily. No patient outcomes reported.

#### **Product Quality Issues**

Case numbers 6761572 v1, 6831683 v1, 7005650 v4, 7581129 v1, 8737910 v2, 8953227 v1 all reported patients who reported passing Isentress tablets in their stool.

Case number 8737910 v2 reported the patient involved in this case had a pepcid ulcer which he had a diverting Ileostomy placed.

Case number 8953227 v1 reported the patient involved in this case also reported frequent stooling, and had an anal fistula. Malabsorption might have been a problem regarding the issue of the product appearing in the stool.

#### **Wrong Frequency Errors**

Case number 8678993 v1 the patient had been taking 2 raltegravir potassium (ISENTRESS) tablets once a day at bedtime. No cause or patient outcomes reported.

Case number 8740277 v2 reported a physician reported several patients' who changed their own Isentress regimen from 400mg BID to 800mg QD when the virus became undetectable

Case number 8775185 v1 reported patients who stated that their physician changed their dose of Isentress from 400 milligrams twice daily to 800 milligrams once daily because the virus became undetectable.

Case number 9144870 v1 reported a patient taking Isentress once a day. No cause or patient outcomes reported.

#### **Wrong Technique Errors**

Case numbers 7581142 v2, 9351541 v1, 8088552 v2, and 8545694 v2 all reported crushing Isentress 400 mg tablets. No causes or patient outcomes reported.

Case number 8880452 v1 reported a patient who was supposed to be taking 1 tablet of the 400 mg twice daily but had been cutting the tablet in half and took two halves of the tablet twice daily.

### **3.2 PROPOSED INSERT LABELING, PATIENT PACKAGE INSERT, AND INSTRUCTIONS FOR USE RISK ASSESSMENT**

#### **3.2.1 Insert Labeling**

After review of the proposed insert labeling, we identified the following vulnerability that may post a risk for medication errors:

##### Dosage and Administration Section of the Full Prescribing Information:

In the “4 weeks (b) (4)” section there is no dose stated. The weight based dose that is presented under Table 2: Recommended Dose for Isentress (b) (4) for Suspension in Pediatric Patients (b) (4)

should be stated in the first bullet such as the following:

- (b) (4)

#### **3.2.2 Patient Package Insert Labeling**

We did not identify any vulnerability in the Patient Package Insert Labeling that would pose a risk for medication errors.

#### **3.2.3 Instructions for Use**

After review of the proposed instructions for use, we identified the following vulnerability that may pose a risk for medication errors:

- The picture in Figure 8 presents a dose of 5 mL. Since all patients may not be prescribed a 5 mL dose, there should be a note indicating that the dose shown may be different than their prescribed dose. This may help mitigate any confusion regarding the correct volume needed to prepare a dose for administration instead of defaulting to the volume in the figure.

### **3.3 CONTAINER LABEL AND CARTON LABELING**

After review of the proposed container label and carton labeling, we identified the following vulnerability with the container label that may post a risk for medication errors:

##### Container Label:

The ‘Opening Instructions’ appear to crowd the principal display panel (PDP) and decreases the prominence of the proprietary and established names.

### **3.4 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT**

After review of the medication error cases retrieved from our FAERS search, we conclude that the insert labeling currently contains clear instructions on dosing and administration, frequency, and technique. Only two of the product quality issue cases

attributed passing of the tablets in the stool to gastrointestinal issues. This is not a labeled occurrence. We will monitor for future product quality issue cases involving passing tablets in the stool and forward the cases to CMC and DQRS if warranted.

We did not identify any issues with the proposed patient package insert labeling. However, we did identify that Figure 8 of the proposed instructions for use needs strengthening to ensure patients do not get confused about what volume they need to prepare a dose for administration. We provide recommendations in Section 4 for issues identified in the proposed insert labeling, the instructions for use, and on the proposed container label.

#### **4 CONCLUSIONS AND RECOMMENDATIONS**

DMEPA concludes that the proposed patient packaging insert labeling, and instructions for use are acceptable from a medication error perspective. However, the insert labeling is unacceptable due to missing dosing information. The container label can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA/ANDA/supplement:

- A. Comments to the Division
  - a. Place the mg/kg dosing [REDACTED] (b) (4) [REDACTED] section of the Dosing and Administration section because there is no dose stated in this section and only refers practitioners to the table for dosing information.
- B. Comments to the Applicant
  - a. Instructions for Use
    - i. In Figure 8, place the below statement after the statement “Open the mixing cup...” to ensure that patients prepare the dose that is prescribed instead of the dose that is presented in the figure:  
“The dose shown in Figure 8 may be different than your prescribed dose.”
  - b. Container Label
    - i. Remove the ‘Opening Instructions’ from the principal display panel (PDP) to avoid overcrowding and place them at the top of the back of the packet.
    - ii. Add the statement “See back panel for opening instructions.” to the PDP.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

## **APPENDICES**

### **Appendix A. Database Descriptions**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

**Appendix B:** Container Labels



**Appendix C:** Carton Labeling



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/s/  
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MORGAN A WALKER  
09/30/2013

JAMIE C WILKINS PARKER  
10/01/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA #	NDA Supplement #:	Efficacy Supplement Type
205786	S-000 (Original NDA)	N/A
22145	S-031	SE-8
203045	S-009	SE-8
Proprietary Name: Isentress Established/Proper Name: raltegravir  Dosage Form: NDA 205786: (b) (4) suspension, 100 mg NDA 22145 S-031: tablets, 400 mg NDA 203045 S-009: chewable tablets, 25 mg and 100 mg  Strengths: see above		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable): N/A		
Date of Application: June 26, 2013 (NDA 205786) June 25, 2013 (NDA 22145 S-031 and NDA 203045 S-009)  Date of Receipt: June 27, 2013 (NDA 205786) June 26, 2013 (NDA 22145 S-031 and NDA 203045 S-009)  Date clock started after UN: N/A		
PDUFA Goal Date: NDA 205786: December 27, 2013 sNDAs 22145/203045: December 26, 2013	Action Goal Date (if different): December 13, 2013	
Filing Date: NDA 205786: August 26, 2013 sNDAs 22145/203045: August 25, 2013	Date of Filing Meeting: August 2, 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): Indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Proposed new dosage form and expansion of patient population to include pediatric patients 4 weeks (b) (4).		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

<b><i>and refer to Appendix A for further information.</i></b>	
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i></b>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input checked="" type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input checked="" type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 69928, 77787				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid*  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p> <p>*Payment not required for efficacy supplements, data is included by reference to NDA 205786</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i></p> <p><b>If yes, please list below:</b></p>																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan</p>		<p>X</p>																		

<p>exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i></p>				
<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><b>If yes, # years requested:</b> 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			Comment from eData group sent on 7/25/13 requesting correction to location of datasets – not a filing issue.
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain.</b></p>	<b>X</b>			
<p><b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>				
<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	X			
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	X			Additional establishment information requested by A. Cuff and submitted by applicant on 7/22/13
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?</p>	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies</i></p>	X			

<i>that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."  If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].  Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)  If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b><u>PREA</u></b>	X			
Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Required pediatric study submitted for ages 4 weeks through 2 years. Other age groups not addressed.
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	X			Additional pediatric information requested, sponsor submitted partial deferral & waiver request on 7/31/2013.
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		It is a partial response to the Written Request (WR) for raltegravir. The WR includes a study in ages 0 to 4 weeks, which has not yet been submitted.
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Consulted to patient labeling, now DMPP.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			DMEPA requested physical samples on 7/25/13.
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>		X		Sponsor references pre-NDA meeting held for NDA 203045 (chewable tablets for pediatric patients 2 to 6 years) on March 15, 2011
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 2, 2013

BLA/NDA/Supp #: NDA 205786  
NDA 22145 S-031  
NDA 203045 S-009

PROPRIETARY NAME: Isentress

ESTABLISHED/PROPER NAME: raltegravir

DOSAGE FORM/STRENGTH:  
NDA 205786: (b)(4) suspension, 100 mg  
NDA 22145 S-031: tablets, 400 mg  
NDA 203045 S-009: chewable tablets, 25 mg and 100 mg

APPLICANT: Merck Sharp & Dohme Corp.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Proposed new dosage form (granules for suspension) to expand the patient population to include pediatric patients ages 4 weeks (b)(4).

BACKGROUND: Merck has submitted NDA 205786 for ISENTRESS (raltegravir) (b)(4) suspension to expand the patient population to include pediatric patients ages 4 weeks (b)(4). Companion efficacy supplements were also submitted to NDA 22145 (S-031) for raltegravir tablets and NDA 203045 (S-009) for raltegravir chewable tablets, as all three NDAs share labeling. The new NDA was submitted in response to PREA PMC 582-3 from the original approval of NDA 22145. Merck is not requesting pediatric exclusivity at this time, as they have not completed the study in neonates that is part of the Written Request.

The submission includes new carton and container labels (b)(4), as well as a new Instructions for Use document that is proposed as part of the patient labeling.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Katherine Schumann	Y
	CPMS/TL:	Elizabeth Thompson	Y
Cross-Discipline Team Leader (CDTL)	Yodit Belew		Y
Clinical	Reviewer:	Brittany Goldberg	Y

	TL:		
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Sung Rhee	Y
	TL:	Jules O'Rear	N
Clinical Pharmacology	Reviewer:	Fang Li	Y
	TL:	Islam Younis Jeffry Florian	Y Y
Biostatistics	Reviewer:	Karen Qi	Y
	TL:	Fraser Smith	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ita Yuen	Y
	TL:	Hanan Ghantous Acting TL Peyton Myers	N Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	NDA 205786: ChunChun Zhang NDA 22145 S-031 & NDA 203045 S-009: Stephen Miller	Y Y
	TL:	Stephen Miller	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	Bryan Riley	N
	TL:	Stephen Langille	N
CMC Labeling Review	Reviewer:		
	TL:		

Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA	Reviewer:	Morgan Walker	Y
	TL:	Jamie Wilkins-Parker	Y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Biopharmaceutics: Kareen Riviere, Reviewer Angelica Dorantes, TL		Y N
Other attendees			

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p> </li> </ul>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>If no, explain:</b></p>	
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b> Comments from eData group on location of datasets sent to Merck on 7/25/2013. Correction expected prior to Filing date, by 8/19/2013.</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> BE inspections will be performed that include verification of virologic endpoints. Given the small numbers of patients at each site, separate clinical inspections are not warranted.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<b>Comments:</b>	
<b>CLINICAL MICROBIOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b> Request for population PK information to be sent as soon as possible.	
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIostatISTICS</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b> At the Filing meeting it was determined that no Biostatistics review will be needed for these applications.	
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b> At the Filing meeting it was determined that no Pharm/Tox review will be needed for these applications.	
<b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b> Biopharmaceutics to provide a request for dissolution information.	
<b><u>Environmental Assessment</u></b>	

<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b> Per the 7/22/13 review by Bryan Riley, the microbial limits specification is acceptable.</p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Review issues for 74-day letter

<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input checked="" type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Jeffrey Muray, MD, MPH, Deputy Director, DAVP

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): September 20, 2013

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

Milestone	Date
Stamp Date	June 26, 2013
Filing/Planning Meeting	August 2, 2013
<b>Filing Date (60-day letter due)</b>	<b>August 25, 2013</b>
74-Day Letter Due	September 8, 2013

<b>Mid-Cycle Meeting</b>	<b>September 20, 2013</b>
Wrap-Up Meeting	November 13, 2013
<b>Primary Reviews Due</b>	PDUFA Goal: December 2, 2013 Internal Goal: <b>November 18, 2013</b>
Labeling & PMR/PMC Discussions	PDUFA Goal: December 5, 2013 Internal Goal: November 20, 2013
CDTL Review Due	PDUFA Goal: December 12, 2013 Internal Goal: November 25, 2013
<b>PDUFA Action Date</b>	PDUFA Goal: December 26, 2013 Internal Goal: <b>December 13, 2013</b>

**Comments:**

### REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

### ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74

<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHERINE SCHUMANN  
08/07/2013

ELIZABETH G THOMPSON  
08/07/2013

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

**Application:** NDA 205786  
NDA 22125 S-031  
NDA 203045 S-009

**Application Type:** New NDA  
Efficacy Supplements

**Name of Drug:** Isentress (raltegravir) (b) (4) suspension, 100 mg  
Isentress (raltegravir) film-coated tablets, 400 mg  
Isentress (raltegravir) chewable tablets, 25 mg and 100 mg

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

**Submission Date:** June 26, 2013 (NDA 205786)  
June 25, 2013 (NDA 22125 S-031 & NDA 203045 S-009)

**Receipt Date:** June 27, 2013 (NDA 205786)  
June 26, 2013 (NDA 22125 S-031 & NDA 203045 S-009)

## 1.0 Regulatory History and Applicant's Main Proposals

Merck has submitted NDA 205786 for ISENTRESS (raltegravir) (b) (4) suspension to expand the patient population to include pediatric patients ages 4 weeks (b) (4). Companion efficacy supplements were also submitted to NDA 22145 (S-031) for raltegravir tablets and NDA 203045 (S-009) for raltegravir chewable tablets, as all three NDAs share labeling. The new NDA was submitted in response to PREA PMC 582-3 from the original approval of NDA 22145. Merck is not requesting pediatric exclusivity at this time, (b) (4)

The submission includes new carton and container labels for the granules, as well as a new Instructions for Use document that is proposed as part of the patient labeling.

The labeling was resubmitted to all three applications on July 11, 2013 to incorporate changes from the recently approved efficacy supplements NDA 22145 S-027 and NDA 203045 S-004.

## 2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## RPM PLR Format Review of the Prescribing Information

### 3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified that will be discussed with the review team during the review period:

1. In the INDICATIONS AND USAGE section of the HIGHLIGHTS, the following statement has been included (b) (4)  
[REDACTED] Per the labeling review tool, “Ordinarily, the absence of information about the safety and effectiveness of a drug in a specific population (e.g. pregnant women, children) should not be included under this heading” which refers to USE IN SPECIFIC POPULATIONS. The review team should be consulted as to a) whether this statement is necessary in the HIGHLIGHTS and b) if the statement is necessary, what is the most appropriate location within the HIGHLIGHTS.
2. The sponsor may want to consider presenting the information under DOSAGE AND ADMINISTRATION in the HIGHLIGHTS in a tabular format, as recommended in the labeling review tool.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter, after consultation with SEALD.

## 4.0 Appendix

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### Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

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### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:** *A waiver was granted for the highlights section length with the approval on NDA 22145 S-22 on December 21, 2011.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

## Selected Requirements of Prescribing Information (SRPI)

Comment:

**YES**

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

Comment:

#### Initial U.S. Approval

**YES**

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

## Selected Requirements of Prescribing Information (SRPI)

### Boxed Warning

- N/A** 12. All text must be **bolded**.  
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).  
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.  
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)  
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).  
Comment:

### Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.  
Comment:
- YES** 18. Must be listed in the same order in HL as they appear in FPI.  
Comment:
- NO** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.  
Comment: *Does not contain the subheading text for 1.2 "Pediatrics." Does not contain the subheading text for 5.2 "Immune Reconstitution Syndrome." Note that Section 5.2 will likely be removed from RMC before the labeling is finalized, as we plan to take action after 08/2013. SEALD will be consulted regarding the need for the subheading text to be included, in addition to the subheading number.*
- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
Comment:

### Indications and Usage

**YES**

## Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

### Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *Bulleted subheadings were used, divided by age groups as opposed to dosage form.*

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

## Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“\*Sections or subsections omitted from the Full Prescribing Information are not listed.”**

Comment:

---

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

### **Contraindications**

- YES** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

### **Adverse Reactions**

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### **Patient Counseling Information**

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KATHERINE SCHUMANN  
08/07/2013

ELIZABETH G THOMPSON  
08/07/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: July 31, 2013

TO: Chief,  
Medical Products & Tobacco Trip Planning Branch  
Division of Medical Products and Tobacco Inspections  
Office of Medical Products and Tobacco Operations

Director, Investigations Branch  
New Orleans District Office  
404 BNA Drive, Bldg. 200, Suite 500  
Nashville, TN 37217

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval  
Data Validation Inspection**, Bioresearch Monitoring,  
Human Drugs, CP 7348.001

RE: NDA 205-786 (Raltegravir granules for suspension),  
NDA 22-145/S-031 (Raltegravir tablets),  
NDA 203-045 (Raltegravir chewable tablets)

SPONSOR: Merck Research Laboratories,  
Whitehouse Station, NJ

This memo requests that you arrange for inspections of the clinical and analytical portions of the following safety/antiviral activity and pharmacokinetic study. **These inspections should be completed prior to** [REDACTED] <sup>(b)(4)</sup>.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) to schedule the inspections. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise. Background material will be available in ECMS under the ORA folder.

**Study #:** IMPAACT P1066 (Merck Protocol 022)  
**Study Title:** "A Phase I/II, Multicenter, Open Label, Noncomparative Study of International

Page 2 - BIMO Assignment, NDA 205-786 (Raltegravir granules for suspension), NDA 22-145/S-031 (Raltegravir tablets), and NDA 203-045 (Raltegravir chewable tablets), sponsored by Merck Research Laboratories

Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Group to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of Raltegravir (Isentress™, MK-0518) in HIV-1 Infected Children and Adolescents"

**Clinical Site #1:** Shandukani Research Wits Reproductive Health & HIV Institute (WRHI)  
██████████<sup>(b)(4)</sup> Hillbrow Health Precinct  
22 Esselen Street, Hillbrow 2001,  
Johannesburg, South Africa  
TEL: 27 082 7466863

**Investigator:** Harry Moultrie, MD  
Email: [hmoultrie@wrhi.ac.za](mailto:hmoultrie@wrhi.ac.za)

**Clinical Site #2:** Department of Pediatrics and Child Health  
Nelson R Mandela School of Medicine,  
University of KwaZulu Natal  
719 Umbilo Road, Durban 4001,  
South Africa  
TEL: 27 031 2604355  
FAX: 27 031 2604388

**Investigator:** Raziya Bobat, MD  
Email: [bobat@ukzn.ac.za](mailto:bobat@ukzn.ac.za)

**Do not reveal the application number, the study to be inspected, the drug name, or the study investigators to the sites prior to starting the inspections.** The sites will receive this information during the inspection opening meetings. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

Once the inspections are completed, **please send a scanned copy of the completed section A of this memo to the DBGLPC POC.**

#### **SECTION A - CLINICAL DATA AUDIT**

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**During the clinical site inspection, please:**

- Confirm the informed consent/assent forms and study records for 100% of subjects enrolled at the site.
- Compare the study records in the NDA submission to the original documents at the site.
- Check for evidence of under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
  - o Number of subject records reviewed during the inspection: \_\_\_\_\_
  - o Number of subjects screened at the site: \_\_\_\_\_
  - o Number of subjects enrolled at the site: \_\_\_\_\_
  - o Number of subjects completing the study: \_\_\_\_\_
- Verify from source documents that case report forms accurately report evaluations related to the primary endpoint.
- Verify the data pertaining to HIV-1 RNA measurements in plasma.**
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocol.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**SECTION B - AUDIT OF ANALYTICAL DATA**

**Analytical Site:**



**Investigator:**

**Methodology:** Liquid and dried blood spot (DBS) samples, LC-MS/MS

**Please complete the following items during the inspection:**

- Examine all pertinent items related to the analytical methods used for the measurement of raltegravir concentrations in human plasma and blood. Analytical methods included assays using liquid and dried blood spot samples.
- Determine if the site employed validated analytical methods to analyze the subject samples.
- Examine data obtained from the cross validation of liquid versus DBS sample assays.
- Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- Compare the assay parameters observed during the study sample analysis with those obtained during method validation. These parameters may include variability between and within runs, accuracy and precision, etc.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.
- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g.,

Page 5 - BIMO Assignment, NDA 205-786 (Raltegravir granules for suspension), NDA 22-145/S-031 (Raltegravir tablets), and NDA 203-045 (Raltegravir chewable tablets), sponsored by Merck Research Laboratories

number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.

- Examine correspondence files between the analytical site and the applicant for their content.

**Additional instructions to ORA Investigator:**

The DBGLPC POC will provide you with compliance program elements, and in certain situations, additional study specific instructions prior to the inspections. Please contact the DBGLPC POC for inspection-related questions and clarifications before, during, and after the inspections.

**If you issue Form FDA 483**, please remind the inspected firm of the 15 business-day timeframe for submission of a written response to observations listed on the form. Promptly fax or email a copy of the form to the DBGLPC POC. If it appears that the site violations may warrant an OAI classification, notify the DBGLPC POC as soon as possible. Fax or email any written response to Form FDA 483 as soon as you receive it to the DBGLPC POC.

DBGLPC POC foreign sites: Arindam Dasgupta, Ph.D.  
Email: [arindam.dasgupta@fda.hhs.gov](mailto:arindam.dasgupta@fda.hhs.gov)  
TEL: (301)796-3326  
FAX: (301)847-8748

DBGLPC POC domestic site: Ruben Ayala, Pharm.D.  
Email: [ruben.ayala@fda.hhs.gov](mailto:ruben.ayala@fda.hhs.gov)  
TEL: (301)796-2018  
FAX: (301)847-8748

Page 6 - BIMO Assignment, NDA 205-786 (Raltegravir granules for suspension), NDA 22-145/S-031 (Raltegravir tablets), and NDA 203-045 (Raltegravir chewable tablets), sponsored by Merck Research Laboratories

cc:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Bonapace/Haidar/Skelly/Choi/Ayala/Dejernett  
ORA/OMPTO/DMPTI/BIMO/Turner/Arline/Carrion/Alexis/Johnson/Braswell/Colon

HFR-SE450/Clarida, Thomas (DIB)

HFR-SE350/Whitten, Krista (BIMO)

CDER/OND/OAP/DAVP/Schumann

CDER/OTS/OCP/DCPIV/Lazor

Draft: RCA 7/31/2013

Edit: MFS 8/1/13

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

ECMS: Cabinets/ORA/OMPTO/BIMO/FY'13/CDER/DMPTI

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**FACTS: 8690285**

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/s/  
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RUBEN C AYALA  
08/02/2013

CHARLES R BONAPACE  
08/02/2013