

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203045Orig1s000**

**OTHER REVIEW(S)**

**Division of Antiviral Products  
Regulatory Project Manager Labeling Review**

**Application Numbers:** 203045 and 22145/S-022

**Name of Drug:** ISENTRESS (raltegravir) Tablets and Chewable Tablets

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

**Labeling Reviewed:**

Last approved supplement (S-020) dated April 22, 2011 and approved November 2, 2011.

NDA 203045 labeling dated December 20, 2011 (SDN 15)

NDA 22145/S-022 labeling dated December 20, 2011 (SDN 628)

**Background and Summary:**

On October 12, 2007, DAVP deferred pediatric study requirements under PREA for ages 2 to 18. NDA 203045 and sNDA 22145/S-022 were submitted to fulfill the PREA PMR for pediatric patients ages 2 to 18 and to provide information regarding pediatric patients in labeling.

Labeling (in SPL format) was submitted electronically to the NDA.

**Review:**

Only major revisions are included in this review. For all revisions, please see attached annotated label.

(b) (4)

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

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

/s/  
-----

ELIZABETH G THOMPSON  
12/21/2011

KAREN D WINESTOCK  
12/21/2011

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA #/Product Name: 203045/Isentress (raltegravir) 25 mg and 100 mg chewable tablets

PMR Description: 1846-1 Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from ages 0 to <4 weeks of age. The study will determine the safety, antiviral activity and pharmacokinetic profile of raltegravir in neonates. The antiviral activity will be based on the results of virologic response over at least 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>December 2012</u>
	Study/Trial Completion:	<u>April 2014</u>
	Final Report Submission:	<u>January 2015</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Pediatric studies should be delayed because the product is ready for approval for use in pediatric subjects 2 to less than 12 years of age and the pediatric studies in the remaining pediatric populations have not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This PMR is a PREA PMR. A deferred pediatric trial evaluating raltegravir for the treatment of HIV-1 infection in pediatric subjects from ages 0 to <4 weeks of age. The study will determine the safety, antiviral activity and pharmacokinetic profile of raltegravir in neonates.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Type of study: a clinical trial evaluating the safety, pharmacokinetic and antiviral activity of raltegravir in pediatric subjects 0 to <4 weeks. The antiviral activity will be based on the results of virologic response over at least 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks when administered for at least 24 weeks.

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

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

/s/  
-----

ELIZABETH G THOMPSON  
12/19/2011

YODIT BELEW  
12/19/2011

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

**PATIENT LABELING REVIEW**

Date: December 1, 2011

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

Through: LaShawn Griffiths, RN, MSHS-PH, BSN  
Team Leader, Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling Reviewer  
**Division of Medical Policy Programs**

From: Latonia M. Ford, RN, BSN, MBA  
Patient Labeling Reviewer  
**Division of Medical Policy Programs**

Subject: DMPP Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): ISENTRESS (raltegravir)

Dosage Form Application Type/Number, Supplement: Film-Coated Tablets NDA 22145/S-022  
Chewable Tablets NDA 203045

Applicant: Merck Sharp & Dohme Corp.

OSE RCM #: 2011-2522

## 1 INTRODUCTION

This review is written in response to a request by the Division of Antiviral Products (DAVP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert for Isentress (raltegravir) Film-Coated Tablets and Chewable Tablets.

On June 30, 2011, Merck Sharp & Dohme Corp. submitted Supplemental New Drug Application (sNDA) 22145/S-022 to expand the indications for Isentress (raltegravir) Film-Coated Tablets (400 mg) to include the treatment of HIV-1 infection in age appropriate pediatric population. In addition, the Applicant seeks approval for NDA 203045 Isentress (raltegravir) Chewable Tablets submitted on June 30, 2011.

Isentress (raltegravir) Tablets, NDA 22145 was originally approved on October 12, 2007 with the last updated approval on November 2, 2011. Isentress (raltegravir) Film-Coated Tablets is approved for the treatment of HIV-1 infection in adult patients.

## 2 MATERIAL REVIEWED

- Draft Isentress (raltegravir) Film-Coated Tablets and Chewable Tablets Patient Package Insert (PPI) received on July 1, 2011 and revised by the review division throughout the current review cycle and received by DMPP on November 18, 2011.
- Draft Isentress (raltegravir) Film-Coated Tablets and Chewable Tablets Prescribing Information (PI) received June 30, 2011, revised by the review division throughout the current review cycle and received by DMPP on November 18, 2011.

## 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 PPI 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 document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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

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

/s/  
-----

LATONIA M FORD  
12/01/2011

BARBARA A FULLER  
12/01/2011

LASHAWN M GRIFFITHS  
12/01/2011

**M E M O R A N D U M**

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

---

DATE: November 22, 2011

TO: Debra Birnkrant M.D.  
Director, Division of Anti-Viral Products (DAVP)

John Lazor, Pharm.D.  
Director, Division of Clinical Pharmacology 4 (DCP4)

FROM: Xikui Chen, Ph.D., Chemist  
Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

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

SUBJECT: Review of EIR Covering NDA 203-045 and NDA 22-145,  
ISENTRESS (Raltegravir Potassium) Adult Tablets (400  
mg) and Chewable Tablets (25, (b) (4) 100 mg),  
Sponsored by Merck Sharp & Dohme Corp.

At the request of DAVP, Division of Bioequivalence and GLP Compliance audited analytical portion of the following study:

**Study Number:** IMPAACT P1066 (Merck Protocol 022)  
**Study Title:** "A Phase I/II, multicenter, open-label, non-comparative 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 analytical portion of the study was conducted at (b) (4)

(b) (4) Following the inspection of (b) (4), Form FDA 483 was issued. As of this writing, we have received no response to the Form FDA 483

observation. Our evaluation of the Form FDA 483 observation follows:

**1. Failure to record the preparations of calibration standards used in 25 bioanalytical runs, and quality control samples used in 3 bioanalytical runs on the Daily Assay Worksheet for raltegravir analyses.**

Preparations of calibration standards used in 25 analytical runs for assay ID from 071003 to 080708, 081219 and 100113, and quality control samples in 3 analytical runs for assay ID 071003, 071004 and 081219 were not referenced on the Daily Assay Worksheet for raltegravir analyses. Preparations of calibration standards and quality control samples were recorded in a laboratory notebook L 40755; however, the preparations were not linked to particular analytical runs. This observation is unlikely to impact the raltegravir assay results.

**Conclusion:**

Following the above inspection, DBGCC recommends that the data for the analytical portion of study IMPAACT P1066 may be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Xikui Chen, Ph.D.

**Final Classification:**

VAI -

(b) (4)

cc:

OSI/Ball/Moreno

OSI/DBGC/Salewski/Dejernett

OSI/DBGC/BB/Haidar/Skelly/Chen

OTS/OCP/DCP4/John Lazor/Ruben Ayala/Sarah Robertson

OND/OAP/DAVP/Debra Birnkrant/Elizabeth Thompson

HFR-SE3555/Patricia S Smith

Draft: 11/18/11

Edits: MFS 11/22/11

OSI: File BE6242

O:\BIOEQUIV\EIRCOVER\203045mer.ral.doc\22145mer.ral.doc

FACTS: 1313530

Email: CDER DSI PM TRACK

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

/s/  
-----

XIKUI CHEN  
11/22/2011

SAM H Haidar  
11/23/2011

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

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

## Memorandum

**Date:** November 21, 2011

**To:** Elizabeth Thompson, M.S., Regulatory Project Manager  
Division of Antiviral Products (DAVP)

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

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

**Subject:** NDA 022145/S-022 – Isentress (raltegravir) Tablets  
NDA 203045 – Isentress (raltegravir) Chewable Tablets

---

As requested in DAVP's consult dated July 15, 2011, DPP and DDTCP have reviewed the Isentress prescribing information (PI), patient package insert (PPI), and carton and container labeling, which have been updated to provide dosage recommendations for pediatric patients 2 years and older, and to include a new chewable tablet dosage form.

DPP's comments are provided directly below in the proposed substantially complete version of the PI sent via email by DAVP on November 16, 2011. DPP has no comments on the carton and container labeling at this time.

DDTCP's comments are provided directly below in the proposed substantially complete version of the PPI sent via email by DAVP on November 16, 2011.

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

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

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

/s/  
-----

JESSICA M FOX  
11/21/2011

SHEETAL PATEL  
11/21/2011

**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 and Labeling Review**

Date: November 15, 2011

To: Debra Birnkrant, MD, Director  
Division of Antiviral Products

Reviewer(s): Walter Fava, RPh, MSED, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD, Team Leader  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Drug Name(s): Isentress (Raltegravir) Chewable Tablets 25 mg and  
100 mg

Application Type/Number: NDA 203045

Applicant/sponsor: Merck, Inc.

OSE RCM #: 2011-2520

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

## **1 INTRODUCTION**

This review evaluates the container labels, carton and insert labeling for Isentress (Raltegravir) Chewable Tablets for NDA 203045. The review responds to a request from the Division of Antiviral Products (DDDP) to review the container labels, carton and insert labeling for this Application.

### **1.1 REGULATORY HISTORY**

Isentress 400 mg tablet was approved in October 2007 and is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients. Merck included the Isentress container label in their revised packaging design for solid oral dosage forms and therefore the container label aligns with their standardized labeling format which DMEPA found acceptable in OSE Review #2010-628-1 dated April 11, 2011.

### **1.2 PRODUCT INFORMATION**

Isentress (Raltegravir) is indicated for the treatment of human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. It will be available as a 400 mg tablet and 25 mg and 100 mg chewable tablets which will be used for patients between the ages of 2 to 11 years of age. The proposed new strengths will be available in bottles of 60 tablets and are to be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F). The chewable tablets are not equivalent to the regular tablet currently marketed.

## **2 METHODS AND MATERIALS REVIEWED**

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

- Container Labels submitted June 30, 2011 (see Appendix A)
- Carton Labeling submitted June 30, 2011 (see Appendix B)
- Insert Labeling submitted June 30, 2011 (no image)
- Currently Marketed container labels of 400 mg tablet (see Appendix C)

Additionally, since Isentress is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Isentress. The AERS search conducted on September 27, 2011 used the following search terms: active ingredient “raltegravir”, trade name “Isentress”, and verbatim terms “raltegravir%” and “Isentress%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitations were set for this search.

---

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

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error.

There were no cases identified relevant to this review.

### **3 CONCLUSIONS AND RECOMMENDATIONS**

#### **3.1 CONTAINER LABELS AND CARTON LABELING**

DMEPA concludes that the proposed labels and labeling could be revised to improve the presentation of the established name. We recommend the following revisions to the carton labeling and container labels to be communicated to the Applicant:

- Revise the statement, [REDACTED] (b) (4), to read, ‘For Pediatric Patients 2 to less than 12 Years of Age’.

#### **3.2 PACKAGE INSERT LABELING**

DMEPA notes areas of improvement for the presentation of information in the Dosage and Administration section to minimize confusion that may lead to dosing errors. Our recommendations are explained in section 3.2.1 and 3.2.2 below.

##### **3.2.1 HIGHLIGHTS OF PRESCRIBING INFORMATION**

###### **A. Dosage and Administration**

1. Include the statement, ‘Isentress can be taken with or without food’ in the Dosage and Administration section.
2. Include the dosing chart from section 2 for pediatric dosing. As currently presented, the dosage and administration information (‘weight based to maximum dose of 300 mg twice daily’), is not specific and does not give healthcare providers an actual dose to use.

###### **B. Warnings and Precautions**

1. Include a statement that chewable tablets should not be substituted for regular tablets.

##### **3.2.2 FULL PRESCRIBING INFORMATION**

###### **A. Dosage and Administration**

1. See Comment 3.2.1.A.1 and revise accordingly.
2. Revise Table 1 and remove th [REDACTED] (b) (4). Presenting [REDACTED] (b) (4) is less confusing. [REDACTED] (b) (4) provides prescribers the option of using [REDACTED]

two 25 mg tablets instead of ½ of a 100 mg tablet for dosing regimens with 50 mg increments.

3. Revise the presentation of the weight range in Table 1 to delete the use of the (b) (4)

[REDACTED] in June 2006, FDA launched a campaign in conjunction with ISMP to prevent the use of error-prone abbreviations in prescribing. As part of this campaign, FDA agreed not to approve such abbreviations in their labeling because these abbreviations are carried on to the prescribing practice.

If you have further questions or need clarifications, please contact Brantley Dorch, Project Manager, at 301-796-0150.

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

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

/s/  
-----

WALTER L FAVA  
11/15/2011

ZACHARY A OLESZCZUK  
11/15/2011

CAROL A HOLQUIST  
11/15/2011

**RPM FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information		
NDA # 203045 NDA # BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type:
Proprietary Name: ISENTRESS Established/Proper Name: raltegravir potassium Dosage Form: chewable tablets Strengths: 25mg and 100 mg		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):		
Date of Application: June 30, 2011 Date of Receipt: June 30, 2011 Date clock started after UN:		
PDUFA Goal Date: December 30, 2011	Action Goal Date (if different):	
Filing Date: August 29, 2011	Date of Filing Meeting: July 28, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): 1. New Dosage Form 2. Expand population to include pediatric patients ages 2-11		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of NDA Supplement: <i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<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"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <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): IND 69,928 and IND 77,787				
<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 Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.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>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
<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><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 (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, 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 exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>X</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			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

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

<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)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?			<b>X</b>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<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>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies 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?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<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?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA 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></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>PREA</b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><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></p>	X			PeRC scheduled for October 12, 2011
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>		X		NDA contains assessment for ages 2-11 only; deferred under PREA for ages 2 and below.

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

<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		
<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>BPCA (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		
<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/DCRMS via the DCRMSRMP 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 type="checkbox"/> Instructions for Use (IFU) <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 in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

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

<sup>4</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<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 PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<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>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
<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)  <i>If yes, specify consult(s) and date(s) sent:</i>		X		
<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>  <i>If yes, distribute minutes before filing meeting</i>		X		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> March 15, 2011  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 28, 2011

**BLA/NDA/Supp #:** NDA 203045

**PROPRIETARY NAME:** ISENTRESS

**ESTABLISHED/PROPER NAME:** raltegravir potassium

**DOSAGE FORM/STRENGTH:** chewable tablets (25mg and 100 mg)

**APPLICANT:** Merck Sharp & Dohme Corp

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** New dosage formulation and expands population to include pediatric patients ages 2 to 11.

**BACKGROUND:** This application was submitted to fulfill PREA commitment number 2 from the October 12, 2007 approval letter for NDA 22145. The new NDA provides for a new dosage formulation and expands the population to include pediatric patients ages 2 to 11.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Thompson	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Yodit Belew		Y
Clinical	Reviewer:	Tafadzwa Vargas-Kasambira	Y
	TL:	Yodit Belew (acting)	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	Sung Rhee	Y
	TL:	Jules O'Rear	Y

Clinical Pharmacology	Reviewer:	Ruben Ayala	Y
	TL:	Sarah Robertson	Y
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ita Yuen	N
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Andrew Yu	Y
	TL:	Rapti Madurawe	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	Andrew Yu	Y
	TL:	Rapti Madurawe	N
Facility Review/Inspection	Reviewer:	Andrew Yu	Y
	TL:	Rapti Madurawe	N
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:	N/A	
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Arzu Selen (Biopharm reviewer) Jessica Fox (DDMAC reviewer) Sheetal Patel (DDMAC reviewer) Latonia Ford (DRISK reviewer) Walter Fava (DMEPA reviewer)		Y N N N Y
Other attendees	Jeff Florian Leslie Chinn Brantley Dorch		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <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> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	
<p><b>Comments:</b></p>	<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
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></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>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined

<p><b><i>If no, for an original NME or BLA application, include the reason. For example:</i></b></p> <ul style="list-style-type: none"> <li>○ <b><i>this drug/biologic is not the first in its class</i></b></li> <li>○ <b><i>the clinical study design was acceptable</i></b></li> <li>○ <b><i>the application did not raise significant safety or efficacy issues</i></b></li> <li>○ <b><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></b></li> </ul>	<p>Reason:</p>
<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> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</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
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Reports are difficult to read. Will ask applicant to re-submit reports using a different font.</p>	<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
<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
<p><b>BIOSTATISTICS</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</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>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<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
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <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 (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input 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 DMPQ?</li> </ul> <p>Comments:</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>Comments:</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>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Jeff Murray, M.D., M.P.H., Deputy Division Director</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<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> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <p><u>Review Classification:</u></p> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<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"/>	If priority review: <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 DMPQ (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"/>	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 at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

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

/s/  
-----

ELIZABETH G THOMPSON  
08/16/2011

KAREN D WINESTOCK  
08/18/2011

# **REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW**

**Application:** NDA 22145/S-022 and NDA 203045

**Name of Drug:** ISENTRESS (raltegravir potassium) tablets and chewable tablets

**Applicant:** Merck Sharp & Dohme

## **Labeling Reviewed**

**Submission Date:** June 30, 2011

**Receipt Date:** June 30, 2011 (NDA 203045) and July 1, 2011 (NDA 22145/S-022)

## **Background and Summary Description**

New Drug Application (NDA 22-145) for ISENTRESS (raltegravir potassium) tablets was approved on October 12, 2007 and included the following pediatric study commitment:

2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 to 18 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.

Protocol submission date: Ongoing

Final Study Report Submission Date: June 30, 2011

The following pediatric study was conducted under IND 69,928 (Merck) and IND 77,787 (NIH) in order to fulfill the above commitment:

IMPAACT P1066/Merck PN022

*"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."*

A Pre-NDA meeting was held on March 15, 2011, to discuss the planned NDA/sNDA which would provide supporting labeling regarding the use of ISENTRESS tablets and chewable tablets in pediatric patients. NDA 22145/S-022 includes proposed labeling for patients ages 6-18. NDA 203045 includes a new dosage form and proposed labeling for patients ages 2-11.

## Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. Applicant included information and telephone number regarding a pregnancy registry in the Highlights section under “Use in Specific Populations” Applicant will be notified to remove this information and replace with the statement “Pregnancy registry available (8.1)”.

## Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by September 12, 2011. The resubmitted labeling will be used for further labeling discussions.

*{See appended electronic signature page}*

---

Elizabeth Thompson, M.S.  
Regulatory Project Manager

Date

---

Karen Winestock  
Chief, Project Management Staff

Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**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).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection 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.”

## Full Prescribing Information (FPI)

### • General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

### • Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

### • Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, 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.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“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.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “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)”

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

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

/s/  
-----

ELIZABETH G THOMPSON  
08/09/2011

KAREN D WINESTOCK  
08/09/2011

MEMORANDUM

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

---

DATE: August 8, 2011

TO: Director Investigations Branch  
New Orleans District  
404 BNA Dr., Bldg 200, Ste. 500  
Nashville, TN 37217 - 2597

FROM: Martin K. Yau, Ph.D.  
Acting Team Leader – Bioequivalence  
Bioequivalence Investigations Branch  
Division of Bioequivalence & GLP Compliance  
Office of Scientific Investigations

SUBJECT: FY 2011, High Priority CDER NDA for pediatric  
indication under Pediatric Research Equity Act (PREA),  
Pre-Approval Data Validation Inspection, Bioresearch  
Monitoring, Human Drugs, CP 7348.001

RE: NDA 203-045 and NDA 22-145 (S-022)  
DRUG: ISENTRESS® (raltegravir potassium) Adult  
tablets (400 mg) and chewable tablets (25, (b) (4)  
100 mg)

SPONSOR: Merck Sharp & Dohme Corp.  
SPONSOR'S AGENT: Robert A. Fromtling, Ph.D.  
Director Worldwide Regulatory Affairs  
126 E. Lincoln Ave  
P.O. Box 2000, RY-33-212  
Rahway, NJ 07065-0900  
TEL: 732-594-4809  
FAX: 732-594-5235

This memo requests that an arrangement be made for a high priority inspection of the analytical portion of the following pivotal pharmacokinetic study in pediatric population. **Due to the PDUFA review due, this inspection should be completed by November 11, 2011.**

**Study Number:** Clinical Trial IMPAACT P0166/Merck PN022

**Study Title:** "A Phase I/II, multicenter, open-label, non-comparative study of the International Maternal, Adolescent AIDS Clinical Trials (IMPAACT) group to evaluate the safety, tolerability, pharmacokinetics, and antiretroviral activity of raltegravir (ISENTRESS, MK-5018) in HIV-1 infected children and adolescents (Protocol 022)"

**Analytical Principal investigator:**

(b) (4)

**Analytical Site:**

**Analytical Method:** LC-MS/MS

All pertinent items related to the analytical method used in the analytical site for the measurement of raltegravir concentrations in human plasma should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submissions should be compared with the original documents at the site. **The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma samples, and the reason for such repetitions should be examined. The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication

Page 3 - (b) (4) Assignment, NDA 203-045 and NDA 22-145 (S-022)  
ISENTRESS® (raltegravir potassium) Adult tablets (400 mg) and  
chewable tablets (25, (b) (4) 100 mg)

between the analytical site and the sponsor should be examined  
for their content.

Following identification of the investigator background material  
will be forwarded directly. **A DBGC scientist with specialized  
knowledge may participate in the inspection of the clinical site  
to provide scientific and technical expertise. Please contact OSI  
upon receipt of this assignment to arrange scheduling of the  
inspection.**

Headquarters' Contact Person: Young M. Choi, Ph.D.  
(301)-796-1516

cc:

CDER OSI PM TRACK

DSI/YMC/Dejernett/CF

HFR-SE350/NOL-DO

HFD-530/Elizabeth Thomson

OCP/DCP-4/John Lazor/Ruben Ayala/Sarah Robertson

Draft: YMC 8/8/11

Edit: MKY 8/9/11

DSI: 6242; O:\BE\assigns\bioNDA203-045-assignment.doc

FACTS: 1313530

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

/s/  
-----

YOUNG M CHOI  
08/09/2011

MARTIN K YAU  
08/09/2011

## DSI CONSULT: Request for BE/GLP Inspections

**Date:** July 13, 2011

**To:** Dr. Sam Haidar  
Dr. Martin Yau  
GLPBB/DSI/Office of Compliance/CDER

**Through:** John Lazor, Pharm.D., Director, DCP4  
Ruben Ayala, PharmD., Clinical Pharmacology Reviewer  
Sarah Robertson, Pharm.D., Clinical Pharmacology TL

**From:** Elizabeth Thompson, M.S., Regulatory Project Manager, DAVP, HFD-530

**Subject:** **Request for Bioanalytical Site Inspection**

### **I. General Information**

Application#: NDA 203-045 and NDA 22-145 (S-022)

Applicant/ Applicant contact information (to include phone/email): Merck Sharp Dohme, Corp.  
Drug Proprietary Name: ISENTRESS

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): Yes

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of HIV-1 infection in pediatric patients ages  $\geq 2$  to <19 years of age

PDUFA: December 30, 2011

Action Goal Date: December 30, 2011

Inspection Summary Goal Date: December 2, 2011

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
BIOANALYTICAL Site:  (b) (4)	Study: IMPAACT P1066/Merck PN022 (Bioanalytical lab only)	44 Subjects with PK data at the proposed dose	Treatment of HIV-1 infection in pediatric patients ages $\geq 2$ to $< 19$ years of age

**III. Site Selection/Rationale**

*Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

The Sponsor submitted one pivotal trial for the approval of Isentress for use in the proposed pediatric population. The trial listed below collected intensive pharmacokinetic data in a subset of pediatric subjects to support approval of the proposed pediatric doses.

1. Clinical trial IMPAACT P0166/Merck PN022 – A phase I/II, multicenter, open-label, non-comparative 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-5018) in HIV-1 infected children and adolescents (Protocol 022)

We are requesting an inspection of the bioanalytical site only. The bioanalytical laboratory at the  analyzed all PK plasma samples for this trial.

Inspection of the clinical sites enrolling PK subjects is not being requested, as too few subjects were enrolled at any one site. A total of 18 sites enrolled intensive PK subjects, with no more than 5 subjects enrolled at any one site.

*Rationale for DSI Audits*

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See\*\*\* at end of consult template for DSI's thoughts on things to consider in your decision making process*

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):  
Significant pharmacokinetic results pertinent to decision-making

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact Elizabeth Thompson at 301-796-0824 or Ruben Ayala at 301-796-2018.

Concurrence: (as needed)

Ruben Ayala, Clinical Pharmacology Reviewer  
Sarah Robertson, Clinical Pharmacology Team Leader  
John Lazor, Division Director, Office of Clinical Pharmacology, Div.4

***Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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

/s/  
-----

ELIZABETH G THOMPSON  
07/14/2011

JOHN A LAZOR  
07/14/2011