

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203045Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 203-045**

**ISENTRESS™ (raltegravir potassium) Chewable Tablets  
25 mg and 100 mg**

**Merck Sharp & Dohme Corp.**

**Andrew Yu, PhD  
ONDQA, Branch V**

**DAVP**

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# Chemistry Review Data Sheet

1. NDA: 203-045
2. REVIEW #2
3. REVIEW DATE: 12/1/11
4. REVIEWER: Andrew Yu
5. PREVIOUS DOCUMENTS:

Previous Documents

NDA 22-145/SCM-007  
NDA 22-145/SUPPL-22

Document Date

31-MAR-2009  
01-JUL-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Amendment (IR- response)

Amendment (IR- response)

Package insert amendment

Response to IR dated 11/22/11

Document Date

6/30/11

(7/28/11 CDER date)

08/25/2011

08/26/2011

09/12/2011

12/1/2011

7. NAME & ADDRESS OF APPLICANT:

:

Name: Merck & Co. Inc.

## Chemistry Review Data Sheet

Address: 126 E. Lincoln Avenue  
P.O. Box 2000, RY33-212  
Rahway, NJ 07065-0900

Contact person: Robert A. Fromtling, Ph.D.  
Director, Worldwide Regulatory Affairs

Telephone: 732-594-4809

Fax 732-594-5235

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ISENTRESS Chewable tablets  
b) Non-Proprietary Name (USAN): Raltegravir Chewable tablets  
c) Code Name/# (ONDQA only): None  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
  - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Chewable tablets

12. STRENGTH/POTENCY: 25 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

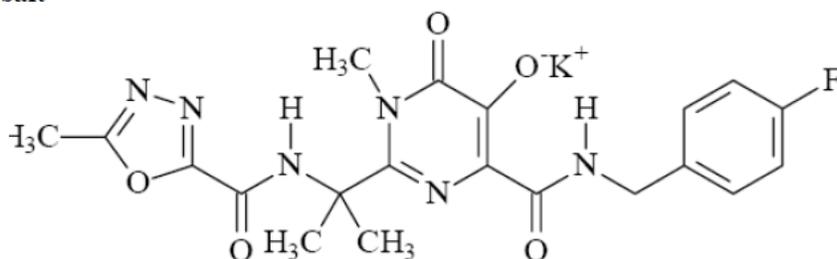
SPOTS product – Form Completed  
 Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN: Raltegravir

N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium

salt



Molecular weight 482.51  
Molecular Formula  $C_{20}H_{20}FKN_6O_5$   
Chemical Abstract [871038-72-1]

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE	COD E <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	Material	Adequate	Reviewed by G. Lunn 27-Aug-2007	
	II			1	Adequate	Reviewed by G. Lunn on 18-Sep-2007	
	III			4	Adequate		
	III			3	Adequate	20-APR-2004 S. Pope	
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

## Chemistry Review Data Sheet

(b) (4)	(b) (4)	(b) (4)	(b) (4)				
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	9/15/11 A. Yu	
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	9/15/11 A. Yu	
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	9/15/11 A. Yu	
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	9/15/11 A. Yu	Review #3
(b) (4)	IV	(b) (4)	(b) (4)	3	Adequate	2-Feb-2000 By K. Swiss	Review #2 for (b) (4)
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
(b) (4)		(b) (4)	(b) (4)				
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference granted

6 – DMF available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did need to be reviewed)

B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall Acceptable	10/13/2011	M. Stock
Pharm/Tox			
Biopharmaceutics	Adequate	12/2/2011	Arzu Selen
LNC			
Methods Validation	Adequate	7/20/11	Andrew Yu
OPDRA (DMETS)	Adequate after changes made	11/15/11	Walter L. Fava
EA	EA exclusion waiver found acceptable	7/20/11	Andrew Yu

19. ORDER OF REVIEW (OGD Only) N/A

# The Chemistry Review for NDA 203-045

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The two IRs outstanding in review #1 have been resolved (appendix II & III) The labels have adequate information with changes submitted to the final label. The recommendation from the Office of Compliance on the manufacturing sites are overall acceptable. Therefore, from the CMC perspective, this NDA is recommended for approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Applicable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug substance:

The drug substance raltegravir potassium is manufactured by Merck Pharmaceuticals Inc., and is referenced by NDA 22-145 and NDA 22-145/SCM-007 and found adequate. The DMFs that reference the (b) (4) for raltegravir potassium, DMF# (b) (4) and DMF (b) (4) are both adequate.

##### Drug product:

NDA 203-045 provides for Raltegravir Chewable tablets, 100 mg and 25 mg, for pediatric use. The 25 mg strength is an un-scored round-shaped tablet while the 100 mg strength is a scored oval-shaped tablet to allow dosing of 50 mg. The applicant's adult strengths of Raltegravir tablets, 400 mg is currently approved. The pediatric chewable tablets are submitted as 505(b)(1) as a new dosage form. After discussion with NDA review team including DMEPA, it was agreed that 'chewable tablet' was the appropriate dosage form for this drug product even though the labeling would offer the option of swallowing tablets without chewing. The pediatric chewable tablets are **not** bioequivalent with the adult tablet.

The pediatric chewable tablet formulation contains adequate sweeteners and flavors for taste masking and other commonly used excipients for tablet formulations. The 5 DMFs (b) (4) are acceptable.

## Executive Summary Section

The manufacturing of the chewable tablets involves (b) (4)

DMFs referenced for (b) (4) are acceptable.

The shelf life of 24 months at controlled room temperature is based on three stability batches of long term stability data for 12 months and additional bridging stability data for increased amount of desiccant in the package. Two of the primary stability batches differ from the commercial batches in manufacturing site, equipment and scale (but within 1/10<sup>th</sup> commercial). The third stability batch and the bridging stability batch are made at the commercial site. The composite stability data provided are adequate to support the proposed shelf life of the commercial material.

CMC review issues related to stability, microbial testing, and product quality have been adequately addressed by the applicant. The list of information requests (IRs) sent to the applicant are given at the end of the review.

The overall control strategy to assure quality for Insentress Tablets are comprised of the following elements:

- a. Control of drug substance:
  - i. Control of particle size to (b) (4).
  - ii. Control of (b) (4) of drug substance to NMT (b) (4).
  - iii. Release testing of drug substance lots for appearance, identity, assay, impurities, (b) (4), particle size, (b) (4) (NDA 22-145).
- b. Control of drug product:
  - i. Identification of critical manufacturing process steps and critical process parameters.
  - ii. (b) (4) adding a total of 4 g desiccant to the container to prevent surface mottling of the chewable tablets and prevent microbial growth.
  - iii. Release testing of drug product batches for appearance (lack of discoloring), identity, assay, chromatographic purity, dose uniformity, and dissolution.

**B. Description of How the Drug Product is Intended to be Used**

ISENTRESS tablets 100 mg are pale orange, oval-shaped, orange-banana flavored, chewable tablets scored on both sides and imprinted on one face with the Merck logo and "477" on opposite sides of the score. ISENTRESS tablets 100 mg is supplied as : NDC 0006-0477-61 unit-of-use bottles of 60.

## Executive Summary Section

ISENTRESS tablets 25 mg are pale yellow, round, orange-banana flavored, chewable tablets with the Merck logo on one side and "473" on the other side. ISENTRESS tablets 25 mg is supplied as: NDC 0006-0473-61 unit-of-use bottles of 60.

Storage and Handling for both the 400 mg Tablets and Chewable Tablets are:  
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature. The chewable tablets should be stored in the original package with the bottle tightly closed. Keep the desiccant in the bottle to protect from moisture. Dosing for the chewable tablets in children are weight based generally given twice daily as indicated in the package insert.

**C. Basis for Approvability or -Approval Recommendation**

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. Outstanding information requests in review #2 are adequately responded. The labels have adequate information with changes submitted to the final label. The recommendation from the Office of Compliance on the manufacturing sites are overall acceptable. Therefore, from the CMC perspective, this NDA is recommended for approval.

**III. Administrative****A. Reviewer's Signature**

See DARRTS

**B. Endorsement Block**

See DARRTS

**C. CC Block**

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/s/  
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ANDREW B YU  
12/05/2011

STEPHEN P MILLER  
12/05/2011

For Rapti Madurawe.  
I concur - this NDA is recommended for approval from the CMC perspective.

**NDA 203-045**

**ISENTRESS™ (raltegravir potassium) Chewable Tablets  
25 mg and 100 mg**

**Merck Sharp & Dohme Corp.**

**Andrew Yu, PhD  
ONDQA, Branch V**

**DAVP**

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B. Environmental Assessment Or Claim Of Categorical Exclusion .....	98
III. List Of Deficiencies To Be Communicated.....	99

# Chemistry Review Data Sheet

1. NDA: 203-045
2. REVIEW #1
3. REVIEW DATE: 10/26/11
4. REVIEWER: Andrew Yu
5. PREVIOUS DOCUMENTS:

Previous Documents

NDA 22-145/SCM-007  
NDA 22-145/SUPPL-22

Document Date

31-MAR-2009  
01-JUL-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Amendment (IR- response)

Amendment (IR- response)

Package insert amendment

Document Date

6/30/11  
(7/28/11 CDER date)

08/25/2011

08/26/2011

09/12/2011

7. NAME & ADDRESS OF APPLICANT:

:

Name: Merck & Co. Inc.

## Chemistry Review Data Sheet

Address: 126 E. Lincoln Avenue  
P.O. Box 2000, RY33-212  
Rahway, NJ 07065-0900

Contact person: Robert A. Fromtling, Ph.D.  
Director, Worldwide Regulatory Affairs

Telephone: 732-594-4809

Fax 732-594-5235

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ISENTRESS Chewable tablets
- b) Non-Proprietary Name (USAN): Raltegravir Chewable tablets
- c) Code Name/# (ONDQA only): None
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antiviral

11. DOSAGE FORM: Chewable tablets

12. STRENGTH/POTENCY: 25 mg and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed  
 Not a SPOTS product

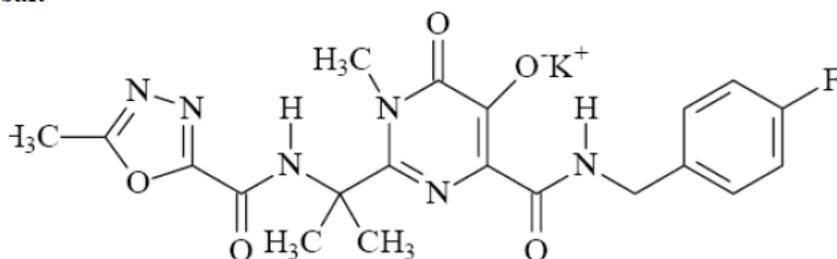
## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

USAN: Raltegravir

N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium

## Chemistry Review Data Sheet

salt



Molecular weight 482.51  
Molecular Formula  $C_{20}H_{20}FKN_6O_5$   
Chemical Abstract [871038-72-1]

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE	COD E <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	Material	Adequate	Reviewed by G. Lunn 27-Aug-2007	
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	Reviewed by G. Lunn on 18-Sep-2007	
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	20-APR-2004 S. Pope	
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		

## Chemistry Review Data Sheet

(b) (4)	(b) (4)					
		III	4	Adequate		
		IV	1	Adequate	9/15/11 A. Yu	
		IV	1	Adequate	9/15/11 A. Yu	
		IV	1	Adequate	9/15/11 A. Yu	
		IV	1	Adequate	9/15/11 A. Yu	Review #3
		IV	3	Adequate	2-Feb-2000 By K. Swiss	Review #2 for (b) (4)
		III	4	Adequate		
		III	4	Adequate		
		III	4	Adequate		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference granted

6 – DMF available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did need to be reviewed)

B. Other Documents: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall Acceptable	10/13/2011	M. Stock
Pharm/Tox			
Biopharmaceutics	Adequate	11/10/2011	Arzu Selen
LNC			
Methods Validation	Adequate	7/20/11	Andrew Yu
OPDRA (DMETS)	Adequate after changes made	11/15/11	Walter L. Fava
EA	EA exclusion waiver found acceptable	7/20/11	Andrew Yu

19. ORDER OF REVIEW (OGD Only) N/A

# The Chemistry Review for NDA 203-045

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Two information requests are still outstanding. All other CMC information provided is adequate. The labels have adequate information with changes submitted to the final label. The recommendation from the Office of Compliance on the manufacturing sites are overall acceptable. A CMC recommendation for NDA approval is not made at this time until satisfactory closure of the pending information requests.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug substance:

The drug substance raltegravir potassium is manufactured by Merck Pharmaceuticals Inc., and is referenced by NDA 22-145 and NDA 22-145/SCM-007 and found adequate. The DMFs that reference the (b) (4) for raltegravir potassium, DMF# (b) (4) and DMF# (b) (4) are both adequate.

##### Drug product:

NDA 203-045 provides for Raltegravir Chewable tablets, 100 mg and 25 mg, for pediatric use. The 25 mg strength is an un-scored round-shaped tablet while the 100 mg strength is a scored oval-shaped tablet to allow dosing of 50 mg. The applicant's adult strengths of Raltegravir tablets, 400 mg is currently approved. The pediatric chewable tablets are submitted as 505(b)(1) as a new dosage form. After discussion with NDA review team including DMEPA, it was agreed that 'chewable tablet' was the appropriate dosage form for this drug product even though the labeling would offer the option of swallowing tablets without chewing. The pediatric chewable tablets are **not** bioequivalent with the adult tablet.

The pediatric chewable tablet formulation contains adequate sweeteners and flavors for taste masking and other commonly used excipients for tablet formulations. The 5 DMFs for (b) (4) are acceptable.

## Executive Summary Section

The manufacturing of the chewable tablets involves (b) (4)

DMFs referenced for (b) (4) are acceptable.

The shelf life of 24 months at controlled room temperature is based on three stability batches of long term stability data for 12 months and additional bridging stability data for increased amount of desiccant in the package. Two of the primary stability batches differ from the commercial batches in manufacturing site, equipment and scale (but within 1/10<sup>th</sup> commercial). The third stability batch and the bridging stability batch are made at the commercial site. The composite stability data provided are adequate to support the proposed shelf life of the commercial material.

CMC review issues related to stability, microbial testing, and product quality have been adequately addressed by the applicant. The list of information requests (IRs) sent to the applicant are given at the end of the review.

The overall control strategy to assure quality for Insentress Tablets are comprised of the following elements:

- a. Control of drug substance:
  - i. Control of particle size to (b) (4).
  - ii. Control of (b) (4) of drug substance to NMT (b) (4).
  - iii. Release testing of drug substance lots for appearance, identity, assay, impurities, (b) (4), particle size, (b) (4) (NDA 22-145).
- b. Control of drug product:
  - i. Identification of critical manufacturing process steps and critical process parameters.
  - ii. (b) (4) adding a total of 4 g desiccant to the container to prevent surface mottling of the chewable tablets and prevent microbial growth.
  - iii. Release testing of drug product batches for appearance (lack of discoloring), identity, assay, chromatographic purity, dose uniformity, and dissolution.

## B. Description of How the Drug Product is Intended to be Used

ISENTRESS tablets 100 mg are pale orange colored, oval-shaped, orange-banana flavored, scored chewable tablets with the Merck logo and "477" on opposite sides of the score and plain on the reverse side. ISENTRESS tablets 100 mg is supplied as : NDC 0006-0477-61 unit-of-use bottles of 60.

## Executive Summary Section

ISENTRESS tablets 25 mg are pale yellow, round, orange-banana flavored, chewable tablets with the Merck logo on one side and "473" on the other side. ISENTRESS tablets 25 mg is supplied as: NDC 0006-0473-61 unit-of-use bottles of 60.

Storage and Handling for both the 400 mg Tablets and Chewable Tablets are:  
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature. The chewable tablets should be stored in the original package with the bottle tightly closed. Keep the desiccant in the bottle to protect from moisture. Dosing for the chewable tablets in children are weight based generally given twice daily as indicated in the package insert.

**C. Basis for Approvability or -Approval Recommendation**

Two information requests are still outstanding. All other CMC information provided is adequate. The labels have adequate information as required. A recommendation from the Office of Compliance on the site acceptability has been made and is overall acceptable. From the CMC perspective, a recommendation for approval is not made at this time until satisfactory closure of the pending information requests.

**III. Administrative****A. Reviewer's Signature**

See DARRTS

**B. Endorsement Block**

See DARRTS

**C. CC Block**

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/s/  
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ANDREW B YU  
11/22/2011

RAPTI D MADURawe  
11/22/2011

Initial Quality Assessment Branch V  
Pre-Marketing Assessment Division II

**OND Division:** Division of Anti-Viral Products  
**NDA:** 203-045  
**Applicant:** Merck  
**Stamp Date:** June 30, 2011  
**Proposed Trademark:** Isentress  
**Established Name:** Raltegravir  
**Dosage Form:** Chewable Tablets  
**Route of Administration:** Oral  
**Strength:** 25 and 100 mg  
**Indication:** Treatment of HIV Infection  
**CMC Reviewer:** Andrew Yu  
**Biopharmaceutics Reviewer:** Arzu Selen  
**CMC Lead:** Steve Miller

**Acceptable for filing:** Yes  
**Comments for 74-Day Letter:** No

## Summary and Critical Issues

### Summary

To support dosing in younger pediatric patients, chewable tablets were developed. The existing adult-strength product is a 400 mg immediate release tablet which is taken twice a day (BID). A supplement was also submitted to the NDA for the adult tablet (22-145 / S-022) to cover revisions of the label (e.g., new dosing information).

The 100 mg chewable tablet is scored to provide flexibility in dosing. The proposed dosing now ranges from (b) (4) BID to 300 mg BID (see table in Labeling, below).

The chewable tablets and the 400 mg adult tablet are not bioequivalent, so patients and prescribers are cautioned in labeling not to substitute them.

### Information from IND and Earlier NDA Development

(b) (4)



For further information, see the two CMC reviews of the original NDA 22-145 submission (G. Lunn and T. Chang).

During PreNDA discussions, FDA agreed to recognize stability data from the Phase III round 50 and 100 mg tablets as the primary stability data to support the intended commercial oval/scored 100 mg tablets. Limited stability data on the oval/scored tablets and dissolution studies would be used to bridge to the stability data on the round tablets.

### **Drug Substances**

(b) (4) are approved and may be used to produce raltegravir DS.

(b) (4) was approved via Supplement 5 on Aug 25, 2009.

NDA 22-145 is referenced for most DS information. The DS specification is included in Module 3. A (b) (4) of DS will be used for the chewable tablets (noted in footnote to specification table).

### **EES Information**

Site info in Module 1 and Module 3 are consistent with the exception of the (b) (4) site listed as 'Release Tester' in Module 1 and 'Release to Distribution' in Module 3.

Comments were put into EES to clarify that the (b) (4) is used at the (b) (4) sites, and the (b) (4) is used at the (b) (4) facilities.

Facilities that only make the (b) (4) were not added to EES.

### **Pharmaceutical Development, Quality Control Strategy including DP Specifications**

To provide adequate taste masking, (b) (4)

Three batches of primary stability and two bridging batches all at (b) (4) of intended commercial scale

Microbial testing is included in the DP specification table, for testing at batch release. There is also info on (b) (4) included in the NDA.

### **Packaging Configuration**

Container Type & Tablet counts	CR Closure (Y/N)	Carton (Y/N)
HDPE bottle of 60 with induction seal and 4 g of desiccant	Y	Y

### **Stability**

Statements on the bottle labels say “Store in the original package with bottle cap tightly closed. Keep the desiccant in the bottle to protect product from moisture.”

30°C/75%RH = long-term condition for primary, bridging, first 3 commercial and yearly protocols.

12-month data on clinical tablets:

- round 25 mg and round 100 mg; with 2 g desiccant

13-week bridging data on proposed commercial tablets:

- round 25 mg and oblong/scored 100 mg; both with 4 g desiccant

24 mo expiry is proposed.

#### **Stability Protocols:**

A full schedule of time points are planned for the first 3 commercial batches (30°/75%RH and 40°/75%RH) and for the yearly commitment (30°/75%RH only as is usual).

The only attributes listed for testing in the commercial protocols are: assay, degradants, dissolution and appearance. Is it appropriate to include microbial limits testing at some time points?

### **Labeling**

At the filing meeting, Dr. Selen raised the question whether the labeling should indicate that tablets must be chewed, or alternatively, that they can be either chewed or swallowed intact. This important question will need input from Clin-Pharm, BP, CMC, DMEPA and clinical perspectives, so it should be discussed at an early multidisciplinary Global Assessment Meeting (GAM).

The protection provided by the container/closure/desiccant system is emphasized by the labeling statement:

“Store in the original package with the bottle tightly closed. Keep the desiccant in the bottle to protect from moisture.”

The bottle labels, carton labels, and the PI show “(raltegravir)” as the established name of the active ingredient, and include the equivalency statement (e.g., “Each tablet contains

108.6 mg raltegravir potassium, equivalent to 100 mg raltegravir.”). This is consistent with the naming of the adult tablet, and with current ONDQA policy. The Patient Product Information sheet does not mention potassium, or contain an equivalence statement (perhaps clarify with DMEPA if this is appropriate?).



There are no instructions in either the Prescribing Information or the Patient Product Information regarding whether the chewable tablets must be chewed, or if they can also be swallowed intact.

**Table 1: Recommended Dose for ISENTRESS Chewable Tablets in Pediatric Patients 2 Through 11 Years of Age**

Body Weight		Dose	Number of Chewable Tablets per dose
(kg)	(lbs)		
10 to < 14	22 to < 31	75 mg twice daily	3 x 25 mg
14 to < 20	31 to < 44	100 mg twice daily	1 x 100 mg
20 to < 28	44 to < 62	150 mg twice daily	1.5 x 100 mg*
28 to < 40	62 to < 88	200 mg twice daily	2 x 100 mg
at least 40	at least 88	300 mg twice daily	3 x 100 mg

\*The 100 mg chewable tablet can be divided into equal halves.

**Early action needed:** An early IR letter was already sent.

**Comments for 74-day letter:** none

**Conclusion and Recommendation:**

Based on this Initial Quality Assessment, this NDA is determined to be complete and therefore filable from CMC perspective. Background information and suggestions for the review are noted in this document. The filing checklist has been completed and was filed separately in DARRTS.

Stephen P. Miller, Ph.D.  
CMC-Lead

See DARRTS  
Date

Rapti Madurawe, Ph.D.  
Branch Chief

See DARRTS  
Date

**Drug Product Composition:**

Raltegravir Chewable Tablet—Market Composition

Component	Quality Reference <sup>3</sup>	Function	Unit strength	
			25 mg mg/tablet	100 mg mg/tablet
Raltegravir†	In-house <sup>II</sup>	(b) (4)	27.16	108.6
Hydroxypropyl Cellulose	USP-NF or Ph. Eur.			(b) (4)
(b) (4)	¶			
(b) (4)	#			
Sucralose	USP-NF or Ph. Eur.			
Saccharin Sodium	USP-NF or Ph. Eur.			
Sodium Citrate, Dihydrate	USP-NF or Ph. Eur.			
Mannitol	USP-NF or Ph. Eur.			
Ferric Oxide, Red	USP-NF			
Ferric Oxide, Yellow	USP-NF			
Monoammonium Glycyrrhizinate	1			
(b) (4)				
Natural Banana Flavor	2			
(b) (4)				
Natural and Artificial Orange Flavor	3			
(b) (4)				
Natural and Artificial Masking Flavor	4			
(b) (4)				
Crospovidone	USP-NF or Ph. Eur.			
Magnesium Stearate	USP-NF or Ph. Eur.			
Sodium Stearyl Fumarate	USP-NF or Ph. Eur.			
Total Tablet Weight			233.3	466.7
				(b) (4)

## Drug Product Specification

Specification Established for Raltegravir Chewable Tablet

Tests	Acceptance Criteria	Test Methods
Appearance (release and shelf-life)	25 mg: Pale yellow, round, flat faced, beveled edge tablet debossed with the Merck logo on one side and 473 on the other  100 mg: Pale orange, oval shaped scored tablet, debossed with the Merck logo on one side of the score and 477 on the other, and plain on the other side of the tablet	Test by visual observation.
Assay (release and shelf-life)	(b) (4)	Assay by HPLC (Sec. 3.2.P.5.2.1)
Degradation Products (release and shelf-life)	Open Ring: NMT (b) (4) Acid: NMT (b) (4) Any Unspecified: NMT (b) (4) Total Degradation Products: NMT (b) (4)	Assay by HPLC (Sec. 3.2.P.5.2.1) see Raltegravir potency assay
Identity by FTIR (release)	The presence of raltegravir is confirmed if sample spectrum's main peaks match those of the reference spectrum	Identity by FTIR (Sec. 3.2.P.5.2.4)
Identity by HPLC (release)	The retention times of the raltegravir peak in the sample and standard chromatograms are essentially the same (within (b) (4)).	Assay by HPLC (Sec. 3.2.P.5.2.1) see Raltegravir potency assay

Content Uniformity (release)	Complies with the requirements of the USP <905> and Ph. Eur. 2.9.40	HPLC (Sec. 3.2.P.5.2.3)
Dissolution (release and shelf life)	Q = (b) (4) dissolved in 15 minutes <sup>†</sup>	HPLC (Sec. 3.2.P.5.2.2)
Microbial Limits (release)	Absence of <i>E. Coli</i> Total Aerobic Microbial Count (b) (4) cfu/g Total Combined Yeast and Mold Count (b) (4) cfu/g	As per Ph. Eur. 2.6.12 and 2.6.13 and USP <61> and <62>

<sup>†</sup>Dissolution will follow the appropriate staged criteria as noted in the current compendia

**Drug Substance Specification**

**Raltegravir Specifications**

Analytical Procedure	Acceptance Criteria	Test Method
Assay by HPLC (Release and Stability)	(b) (4)	HPLC – Sec. 3.2.S.4.2.1-0518
Characteristics (Release and Stability)	White to off-white powder	Test by visual observation
Identity by IR (Release)	The sample IR spectrum exhibits maxima in absorbance only at the same wavelengths as those of an authentic sample	IR – Sec. 3.2.S.4.2.5-0518
Identity by Flame Test (Release)	The sample imparts a violet color to the flame indicating the presence of potassium	Flame Test – Sec. 3.2.S.4.2.4-0518
Impurities by HPLC (Release and Stability)	Maximum (b) (4) Area Maximum (b) (4) Area	HPLC – Sec. 3.2.S.4.2.1-0518
(b) (4)		
Particle size † (Release)	(b) (4) microns Mean (b) (4) microns	PSD- Sec. 3.2.S.4.2.6-0518
† Particle size used in the chewable tablet (b) (4) will be limited to a mean between (b) (4) microns. For Justification see Sec. 3.2.P.2.1.1 of the chewable tablet NDA.		

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/s/  
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STEPHEN P MILLER  
08/12/2011

RAPTI D MADURawe  
08/15/2011

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**

**FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>NDA Number:</b>	<b>NDA Type:</b>	<b>Established/Proper Name:</b>
203-045	Original NDA, 505(b)(1)	Isentress (raltegravir) Chewable Tabs, 25 and 100 mg
<b>Applicant:</b>	<b>Stamp Date: June 6, 2011</b>	<b>GRMP Goal: Dec 6, 2011</b>
Merck		<b>PDUFA Goal: Dec 30, 2011</b>

**CMC Reviewer: Andrew Yu, Ph.D.**

**Biopharmaceutics Reviewer: Arzu Selen, Ph.D.**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		All relevant manufacturing sites are described in Section 1.1.2
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		All relevant manufacturing sites are described in Module 3 Section P3 and in Section 1.1.2

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		On follow-on page to 356h form.

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical Exclusion (concentration will remain below 1 ppb) requested in Section 1.12.14

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?		X	Refers to the NDA 22-145 for this information
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to the NDA 22-145 for this information
14.	Does the section contain information regarding the characterization of the DS?		X	Refers to the NDA 22-145 for this information
15.	Does the section contain controls for the DS?	X		DS Specification Table is included
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to the NDA 22-145 for this information
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Limited discussion in 3.2.P.2
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	See reviews of NDA 22-145 by T. Chang and G. Lunn

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**

**FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Narrative description of the process is included in Module 3
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		In 3.2.P.3.4
21.	Is there a batch production record and a proposed master batch record?	X		Four executed batch records are provided for the tablets, including one "bridging" batch for the scored 100 mg tablet. <span style="float: right;">(b) (4)</span>
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		In Sections 3.2.P.2.1
23.	Have any Comparability Protocols been requested?		X	None included in Regional Info
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		Bottles of 60 tablets
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		12-mo (primary) and 13-week (bridging) to support 24 mo proposed expiry; 30°C/75%RH long-term condition
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		Significant process understanding is included in the 90-page section 3.2.P.2.3
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	4	(b) (4)	(b) (4)	Feb 15, 2011	(b) (4)
	4			Feb 7, 2011	
	4			Feb 17, 2011	
9 other Type 3 DMFs are listed in section 1.4.1 for various packaging components					

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		Section 1.14
33.	Have the immediate container and carton labels been provided?	X		Bottle and Carton Labels for 60 tablets (both strengths)

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>J. BIOPHARMACEUTICS</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	Does the application contain dissolution data?	X		Dissolution method and data in NDA 203-045 for Isentress (raltegravir) chewable tablet are adequately described in 3.2.P.2.3.  Additional note: Raltegravir is also identified as a BCS II compound (low solubility, high permeability based on permeability assessment using rat jejunum; please see 2.7.1 and 3.2.P.2.2.3).
35.	Is the dissolution test part of the DP specifications?	X		The proposed dissolution specification for raltegravir chewable tablets (25-mg and 100-mg) is Q = (b)(4) at 15 minutes. (3.2.P.5.1)
36.	Does the application contain the dissolution method development report?	X		Proposed dissolution method for the raltegravir chewable tablets: USP 2, 50 rpm. Medium: 900 mL of water at 37 (b)(4) °C. (Please see 3.2.P.5.3.2)
37.	Is there a validation package for the analytical method and dissolution methodology?	X		Module 3.2.P.5.3. includes validation for analytical procedures (HPLC assay), dissolution, HPLC procedure for dose uniformity and FTIR for identity.
38.	Does the application include a biowaiver request?		X	
39.	Does the application include a IVIVC model?		X	
40.	Is there any <i>in vivo</i> BA or BE information in the submission?	X		This part of the submission will be reviewed by the Office of Clinical Pharmacology.

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small Molecule)**  
**FILING REVIEW FOR NDA or Supplement (ONDQA)**

K. FILING CONCLUSION				
	Parameter	Yes	No	Comment
41.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
42.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Fileable
43.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Fileable
44.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		X	Early CMC information requests have been sent. There are no comments from the CMC or Biopharmaceutics perspectives for the 74-day letter.

*{See appended electronic signature page}*

Stephen Miller, Ph.D.  
 CMC-Lead  
 Division of Pre-Marketing Assessment II, Branch V  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Arzu Selen, Ph.D.  
 Biopharmaceutics Reviewer  
 Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Angelica Dorantes, Ph.D.  
 Biopharmaceutics Team Lead  
 Office of New Drug Quality Assessment

Date

**PRODUCT QUALITY - CMC AND BIOPHARMACEUTICS (Small  
Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

*{See appended electronic signature page}*

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Rapti Madurawe, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment II, Branch V  
Office of New Drug Quality Assessment

Date

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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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STEPHEN P MILLER  
08/12/2011

ARZU SELEN  
08/12/2011

ANGELICA DORANTES  
08/12/2011

RAPTI D MADURAWA  
08/15/2011