CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-145

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: October 5, 2007

To: NDA 22-145

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-145 Isentress (raltegravir) Tablets

I have assessed the ONDQA review of NDA 22-145 and concur with the approval recommendation from a CMC perspective.

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

/s/

Elaine Morefield
10/5/2007 09:20:00 AM
CHEMIST

NDA 22-145

ISENTRESS (raltegravir) Tablets

Merck & Co. Inc.

George Lunn, Ph.D.
Division of Anti-Viral Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-145

2. REVIEW #: 1

3. REVIEW DATE: 18-Sep-2007

4. REVIEWER: George Lunn, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
RRZ-001	12-Jan-2007
RRZ-002	31-Jan-2007
RRZ-003	28-Feb-2007
Amendment 0004 (FG)	13-Apr-2007
Amendment 0005 (BC)	30-Apr-2007
Amendment 0035 (BC)	27-Jul-2007
Amendment 0048 (BC)	10-Aug-2007
Amendment 0049 (BC)	16-Aug-2007
Amendment 0061 (BC)	17-Sep-2007

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Merck & Co. Inc.
Address:	126 E. Lincoln Avenue P.O. Box 2000, RY33-212 Rahway, NJ 07065-0900
Representative:	Robert A. Fromtling, Ph.D. Director, Worldwide Regulatory Affairs
Telephone:	732 594 4809

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ISENTRESS
b) Non-Proprietary Name (USAN): Raltegravir potassium
c) Code Name/# (ONDC only): MK-0518
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: HIV Integrase Inhibitor

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 400 mg

13. ROUTE OF ADMINISTRATION: Oral

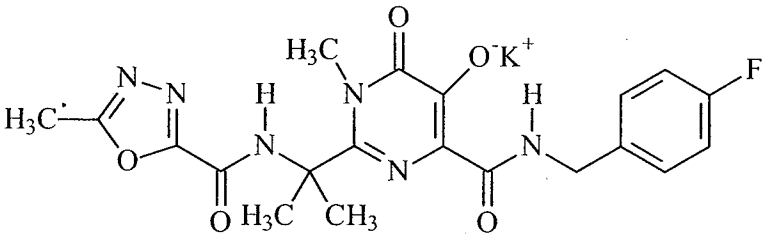
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X____Not a SPOTS product

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

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 Formula: $C_{20}H_{20}FKN_6O_5$
Molecular Weight: 482.51
CAS Registry Number: [871038-72-1]

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					Adequate	09-May-2007	Reviewed by G. Lunn
					Adequate	11-May-2007	Reviewed by G. Lunn
					Adequate	27-Aug-2007	Reviewed by G. Lunn
					Adequate	18-Sep-2007	Reviewed by G. Lunn
					N/A		
					N/A		
					N/A		

		Plastic	closure			
					N/A	
					N/A	
					N/A	
					N/A	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not 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 not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER

REVIEWS			
Biometrics	N/A		
EES	Acceptable	9/5/07	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Not required		
OPDRA	N/A		
EA	Categorical exclusion claimed. Claim accepted.		
Microbiology	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-145

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective. All CMC issues have been satisfactorily resolved and an overall recommendation of Acceptable has been made by the Office of Compliance.

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

None

II. Summary of Chemistry Assessments

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

Raltegravir is an HIV integrase inhibitor. It is the first in its class.

The drug substance is the potassium salt, raltegravir potassium, and it is a white to off-white powder that is not h[redacted] Aqueous solubility is [redacted], and the pH of a saturated solution is [redacted]

The drug substance will be manufactured by Merck Sharp & Dohme (Ireland) Ltd. at Clonmel, Ireland and tested on stability at Merck & Co., Inc., Wilson, NC.

For a detailed review of the manufacturing procedure (S.2) see the separate review by Ted Chang.

The structure is elucidated by spectroscopic techniques. Interpreted UV, IR, ^{1}H NMR, ^{13}C NMR, and mass spectra are provided. The structure is also shown by [redacted] crystallography.

A number of impurities have been identified. The origins of these impurities have been identified and appropriate limits have been set. No degradants were observed after 36 months at 25°C/60% RH, 6 months at 40°C/75% RH, and ICH photostability testing.

The drug substance specifications include tests for appearance, identity, assay, impurities, residual solvents, water, and particle size. The analytical methods are adequately described and have been validated. A satisfactory justification of the specifications is provided and the specified impurities are toxicologically qualified.

Batch analyses are provided for [redacted] laboratory-scale lots produced using the initial process, [redacted] pilot-scale lots produced using the second generation process, and [redacted] lots produced using commercial process.

During the manufacture [redacted]

The drug substance is packaged in [redacted] bags closed with twist ties inside a [redacted] drum. For one batch manufactured using the initial process 36 months of satisfactory stability data obtained at 25°C/60% RH are provided. Similarly for one batch manufactured using the second generation process 24 months of satisfactory data are provided and for 3 batches manufactured using the commercial process 12 months of satisfactory data are provided. For each batch 6 months of satisfactory data obtained at 40°C/75% RH are also provided. [redacted] is assigned and is acceptable.

The drug product for domestic use is a pink film coated tablet that contains 434.4 mg raltegravir potassium, equivalent to 400 mg of the free phenol.

Inactive ingredients are microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic, anhydrous, hypromellose 2208, poloxamer 407, sodium stearyl fumarate, and magnesium stearate. The tablets are film coated using [redacted] Pink [redacted] The components of the film coat are polyvinyl alcohol [redacted] titanium dioxide, PEG 3350, talc, red iron oxide, and black iron oxide. The inactive ingredients, except for the film coats, are compendial. The film coats are comprised of compendial materials. Lactose is derived

from milk collected from healthy animals in the same manner as milk for human consumption and sodium stearyl fumarate and magnesium stearate are of vegetable origin.

For a review of the Pharmaceutical Development Report (P.2) see the separate review by Ted Chang.

The tablets, both domestic (pink) [redacted] will be manufactured, packaged, and released by Merck & Co., Inc., Elkton, VA and stability testing for both will take place at Merck & Co., Inc., Wilson, NC. An EES request was submitted and an Overall Recommendation of Acceptable has been made.

For a review of the manufacturing process (P.3) see the separate review by Ted Chang.

Acceptable specifications for appearance, identity, assay, impurities, dose uniformity, and dissolution are provided. The dissolution acceptance criterion in the initial submission was Q = [redacted]% at 60 min. Human trials of the [redacted] tablet showed high peak plasma concentrations and so an erodible tablet was developed to reduce C_{max} and extend T_{max}. Thus the relatively slow dissolution appears to be important and, in response to a request from FDA, the sponsor agreed to add a second dissolution acceptance criterion of ≥ [redacted], at the 15 min time point. The analytical methods are described in detail and have been validated. A justification of the specifications is provided.

Satisfactory batch analyses are provided for [redacted] batches manufactured at [redacted] and [redacted] batches manufactured at [redacted]

The tablets are packaged 60-count in white [redacted] bottles fitted with induction seals and child-resistant closures and containing [redacted] gel canisters. Copies of the container labels are supplied.

Eighteen months of satisfactory stability data obtained at 25°C/60% RH and 30°C/65% RH and 6 months of satisfactory stability data obtained at 40°C/75% RH are provided for 3 batches manufactured at more than [redacted] of the planned maximum batch size. There are no out of specification results and no obvious trends. [redacted]

Photostability testing was carried out in the light cabinet in accordance with ICH Q1B, Option 2 for both the pink [redacted] tablets. No significant change was found. Supporting stability data are presented for a batch with [redacted] film-coating. The tablets were stored at 30°C/65% RH for 108 weeks and at 40°C/75% RH for 26 weeks. There are no out of specification results and no trends of any kind. The sponsor proposes an expiration dating period of 30 months and the

storage statement "Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (see USP Controlled Room Temperature)". This expiration dating period is acceptable for both the domestic (pink) and ——— tablets.

The sponsor requests a categorical exclusion from the requirements to prepare an Environmental Assessment on the grounds that expected introduction concentration will be less than 1 ppb.

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

Isentress (raltegravir) tablets are indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. The recommended dose is one tablet twice daily with or without food. The tablets are supplied in 60-count white ——— bottles fitted with induction seals and child-resistant closures and containing —gel canisters. The storage recommendation is "Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (see USP Controlled Room Temperature)". The expiration dating period is 30 months.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing, and controls for raltegravir drug substance are appropriate. The composition, manufacturing process, and specifications for the tablets are appropriate and the expiration dating period of 30 months when stored at 20-25°C is supported by adequate data. The container-closure system and labeling are appropriate. All manufacturing sites have been found to be acceptable. This NDA is therefore recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

George Lunn, Ph.D. {Signed Electronically in DFS}

B. Endorsement Block

{Signed Electronically in DFS}

C. CC Block

Stephen P. Miller, Ph.D.
Pharmaceutical Assessment Lead

50 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

George Lunn
9/26/2007 02:01:06 PM
CHEMIST

CMC review except for S2, P2, and P3

Norman Schmuff
9/26/2007 02:49:32 PM
CHEMIST