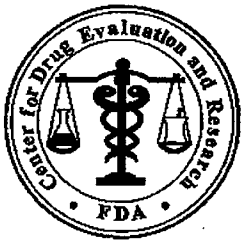
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-145

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	10/12/2007
To:	Monica Zeballos, Regulatory Project Manager Division of Antiviral Products
From:	Melissa Truffa, Safety Evaluator Team Leader Division of Drug Risk Evaluation
Subject:	Raltegravir post marketing commitment
Drug Name(s):	Isentress (Raltegravir)
Application Type/Number:	NDA 22-145
Applicant/sponsor:	Merck & Co, Inc
OSE RCM #:	2007-1993

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1 INTRODUCTION

Office of Surveillance and Epidemiology (OSE) received a consult dated September 18, 2007 requesting comments regarding the concept sheet for the raltegravir protocol for an active surveillance program in response to the risk management review from OSE dated August 24, 2007.

2 MATERIAL REVIEWED

Active Surveillance Program concept sheet for Raltegravir (Isentress)

3 DISCUSSION

4 CONCLUSIONS AND RECOMMENDATIONS

This concept sheet is acceptable; however we need to see the specifics to assess whether the databases chosen are appropriate to address the long term safety concerns. OSE will review the complete protocol when submitted by sponsor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Immediate Office (Risk Management Group)
Office of Surveillance and Epidemiology
Attention: Melissa Truffa and Nancy Clark

FROM: Monica Zeballos, Pharm.D., Regulatory Project Manager
Division of Antiviral Products
Phone (301)796-0840

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Sept 18, 2007		22-145	Concept Sheet for the Active Surveillance Program, which is part of the Risk Management Plan submitted for OSE review in April 2007	Sept 17, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Raltegravir Potassium (MK-0518) Approved trade name: Isentress	ASAP	7030210 Antiviral/systemic/ HIV/ integrase inhibitor	**As soon as possible, please**

NAME OF FIRM: Merck & Co., Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Your review dated Aug 24, 2007 for the RMP recommended that we request the protocol for the Active Surveillance Program. and is not able to submit a written protocol at this time but it submitted a Concept Sheet for this protocol. Please review this Concept Sheet and provide your feedback ASAP. We appreciate a quick turn around give the upcoming PDUFA due date of October 12, 2007.**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Monica Zeballos	☒ MAIL (DFS) ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Monica Zeballos
9/18/2007 05:31:25 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 24, 2007
To:	Debra Birnkrandt, M.D., Director Division of Antiviral Products (DAVP)
Thru:	Ellis Unger, M.D., Acting Deputy Director Office of Surveillance and Epidemiology (OSE)
From:	OSE Risk Management Team Suzanne Berkman, Pharm.D., Senior Drug Risk Management Analyst, OSE-IO Todd Bridges, R.Ph., Team Leader, DMETS Claudia Karwoski, Pharm.D., Risk Management Team Leader, OSE-IO Melissa Truffa, R.Ph., Safety Evaluator Team Leader, DDRE Mary Willy, Ph.D., Epidemiologist, Risk Management Team, OSE-IO
Subject:	OSE RMP Review
Drug Name(s):	Isentress (raltegravir potassium) Tablets
Application Type/Number:	22-145
Applicant/sponsor:	Merck & Co., Inc.
OSE RCM #:	2007-957

1 INTRODUCTION

This review follows a request from the Division of Antiviral Products (DAVP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed risk management plan (RMP) for Isentress (raltegravir potassium) 400 mg Tablets dated April 13, 2007.

Isentress (raltegravir potassium) is an HIV integrase strand transfer inhibitor. Raltegravir is a first-in-class oral agent to be administered as one, 400 mg tablet twice daily. FDA designated raltegravir as fast track on November 9, 2005, and granted priority review.[1] The proposed indication is for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Raltegravir must be used in combination with other anti-retroviral agents. The sponsor has submitted two phase 2 (Protocols 004 and 005) and two phase 3 (Protocols 018 and 019) studies to support the new drug application. As of the April submission, 797 patients had been exposed to raltegravir for greater than 24 weeks, and 221 patients for more than 48 weeks.

2 MATERIAL REVIEWED

The following materials were reviewed:

- Hamilton-Stokes, D. DMETS Proprietary Name Review. Signed July 20, 2007, by C. Holquist.

3 SAFETY CONCERNS

3.1 SPONSOR SAFETY CONCERNS

The sponsor has identified the following safety concerns:

- Immune Reconstitution Inflammatory Syndrome (IRIS): The sponsor reports 3 cases of IRIS (2 in double-blind phase, 1 in open-label phase) and all were documented as serious adverse events. Two of the patients recovered. The third patient died due to hepatocellular carcinoma. There were no cases in the placebo/comparator group.
- Drug Resistance: The sponsor reports the occurrence of drug resistance as follows:
    - Protocol 004: One patient out of 28 exposed to raltegravir in the 10 day monotherapy part of this study had evidence of mutation. During the second part, 5 patients out of 160 (3.1%) had virologic failure. Two of these patients had mutations.
    - Protocol 005: Thirty-eight of 133 (28.6%) had virologic failure. Of these, 35 patients had resistance-related integrase mutations.
    - Protocol 018 and 019: Out of 462 patients treated with raltegravir, 76 had virologic failure (16.5%). Genotyping was sent on 39 of these patients and 27 had treatment-related integrase mutations.
- Drug Interactions with rifampin, phenytoin, phenobarbital; other strong uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) inducers: Co-administration of raltegravir with drugs that strongly induce UGT1A1 may increase metabolism of raltegravir and may reduce raltegravir plasma concentrations and could decrease its therapeutic effect. For example, co-administration with rifampin resulted in 40% lower AUC and C_{max} values. It is interesting to note that raltegravir does not appear to be a substrate for, inhibit, or induce cytochrome P450 enzymes.

[1] Birnkrant, D. Filing Communication letter to Merck signed June 26, 2007.

The sponsor acknowledges the following potential risk:

- Malignancies: Page 21 of the sponsor submission states that 21 adverse events concerning cancer occurred in 20 patients. However, page 24 states that from Protocols 004, 005, 018, and 019, there were 10 (1.3%) patients with neoplasms in the raltegravir group and 1 (0.3%) patient in the comparator group. The mean follow-up duration was approximately 35 weeks for raltegravir group (508 patient years) and 27 weeks for the comparator group (169 patient years). The relative risk is 3.328 (CI 0.47, 144.45). Two additional patients had events during the open-label portion of the studies resulting in 12 (1.4%) patients vs 1 (0.3%) patient.

3.2 DAVP SAFETY CONCERNS

In an internal meeting on August 15, 2007, DAVP presented a review of potential safety concerns.

- Malignancy: Twenty-four patients with 26 malignancies have been documented per the most recent safety update report provided by the sponsor (July 9, 2007). Neoplasms were documented in 19 patients (N=758, 2.5%, 820 patient years (2.3 per 100 patient years)) treated with raltegravir, eight of which were recurrent. Five patients (N=323, 1.5%, 261 patient years (1.9 per 100 patient years)) treated with comparator/placebo had documented cases, two of which were recurrent.
- IRIS: Currently, the medical officer has identified 53 potential IRIS events in 51 patients based on the selection of IRIS-related preferred terms.[2] Forty-two patients (5.6%) in the raltegravir arm were identified in comparison to 11 (3.4%) in the placebo/comparator arm. The medical officer stated that this imbalance is not unexpected given the anticipated immune reconstitution with initiating a new antiviral.

In addition to malignancy and IRIS, the medical officer reviewed a number of other adverse events such as death, rash, hypersensitivity, hepatic, increased CPK, abdominal, cardiovascular, renal, lipid, psychiatric, and erectile dysfunction. At this time, DAVP has not identified any particular trends among any of these adverse events that elicit concern.

3.3 OSE SAFETY CONCERNS

OSE has not identified any additional safety concerns that warrant consideration of a risk minimization action plan (RiskMAP) at this time.[3] However, based on the adverse events reported in the clinical trials, the Division of Drug Risk Evaluation (DDRE) has identified a few adverse events (i.e., increased CPK, rash, hepatic abnormalities, and abdominal adverse events) to pay particular attention to in the post-marketing phase.

4 PROPOSED RISK MANAGEMENT PLAN

The sponsor proposes labeling

[2] The preferred terms included IRS, herpes zoster, CMV infection, cryptococcal meningitis, tuberculosis, mycobacterial infection, PCP, and PML. The FDA review notes 2 raltegravir patients and 1 placebo/comparator patient with the preferred term "IRS" which is consistent with the number in the sponsor RMP submission. However, the sponsor reports no cases in the placebo/comparator arm.

[3] DMETS reviewed the medication errors that occurred in the clinical trials and determined that the factors which contributed to these errors were unique to clinical trials. Therefore, based on the evidence thus far, DMETS does not believe raltegravir is associated with an increased potential for medication error.

populations. The sponsor proposes an enhanced pharmacovigilance approach to monitor for malignancies in addition to labeling (Adverse Reactions section). It is difficult to comment on the proposal given the limited information provided describing the proposed active surveillance program.

6 CONCLUSIONS

The proposal does not constitute a formal RiskMAP. The risks identified by the sponsor - IRIS, drug resistance, and drug interactions - are common to HIV antiviral drug products/multi-drug treatment regimens (i.e., HAART) and are well-known to prescribers. Typically, these risks are managed through routine pharmacovigilance activities consistent with the plan outlined by the sponsor. Based on the information provided, this approach seems reasonable at this time. We

We are unable to determine from the vague outline provided if the proposed active surveillance program for malignancy would be appropriate. If DAVP is sufficiently concerned about the imbalance of malignancies in patients treated with raltegravir, we recommend requesting the protocol for the active surveillance program and consulting an epidemiologist in the Division of Drug Risk Evaluation (DDRE) to review the proposal.

Should DAVP raise further concerns with the risks outlined above or identify additional risks associated with raltegravir warranting more extensive risk management activities or a formal RiskMAP, please send a consult to OSE Risk Management Team.

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/s/

Mary Dempsey
8/24/2007 12:26:56 PM
DRUG SAFETY OFFICE REVIEWER

Ellis Unger
8/24/2007 05:14:33 PM
MEDICAL OFFICER

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mailstop 4447)

DATE RECEIVED: March 7, 2007 **DATE OF DOCUMENT:** February 13, 2007	**DESIRED COMPLETION DATE:** April 18, 2007 **PDUFA DATE:** October 12, 2007	**OSE REVIEW #:** 2007-962

TO: Debra B. Birnkrant, MD
Director, Division of Anti-Viral Products
HFD-530

THROUGH: Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support

FROM: Deveonne Hamilton-Stokes, RN, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Isentress**
(Raltegravir Potassium) Tablets
400 mg

IND# **69,928**
NDA # **22-145**

SPONSOR: Merck & Co., Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Isentress. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

3. Comments pertaining to the RiskMAP will be forwarded in a separate review from OSE.

4. DDMAC finds the proprietary name, Isentress, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence to the sponsor pertaining to this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact OSE Project Manager, Tanya Clayton, Project Manager, at 301-796-0871.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Drug Risk Evaluation (DDRE)
Office of Surveillance and Epidemiology
Attention: Melissa Truffa

FROM: Monica Zeballos, Pharm.D., Regulatory Project Manager
Division of Antiviral Products
Phone (301)796-0840

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 23, 2007		22-145	New NDA with Risk Management Plan in electronic CDT format	April 13, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Raltegravir Potassium (MK-0518) Proposed trade name: Isentress	ASAP (This will go to Advisory Committee on Sept. 5, 2007)	7030210 Antiviral/systemic/ HIV/ integrase inhibitor	**August 13, 2007 (3 weeks prior to Pre-Approval Safety Conference)**

NAME OF FIRM: Merck & Co., Inc.

REASON FOR REQUEST

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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **This is a new NDA with a 6-month review clock submitted in a rolling review fashion (5 pieces) with a Risk Management Plan (RMP) that the Division of Antiviral Products would like OSE to review. The PDUFA action date is October 12, 2007 and the Advisory Committee meeting on Sept. 5, 2007. Please contact Monica Zeballos if you have any questions regarding this NDA. Note: this NDA is completely electronic and in eCTD format, thus it is recommended to use the Global Submit (GS) review tool. The RMP was submitted on April 13, 2007 and is located on the EDR (http://cdernet/edr/) or using the following link: \\CDSESUB1\EVSPROD\NDA022145\022145.enx (make sure you copy and paste either links in the internet explorer address box).**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Monica Zeballos	☒ MAIL (DFS) ☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Monica Zeballos
4/23/2007 05:02:14 PM