

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206510Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 206510	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Dutrebis lamivudine/raltegravir Established/Proper Name: lamivudine/raltegravir Dosage Form: Tablet Strengths: 150mg, 300mg		
Applicant: Merck Sharp & Dohme Corp		
Date of Receipt: April 8, 2014		
PDUFA Goal Date: February 8, 2015	Action Goal Date (if different): February 6, 2015	
RPM: Mammah Borbor		
Proposed Indication(s): HIV-1		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Epivir (lamivudine)	FDA previous findings and safety and efficacy – approved package insert for lamivudine

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The BA/BE studies are comparing the individual products to the fixed dose product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

ISENTRESS (Raltegravir)

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Epivir (lamivudine)	20564	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If “**YES**”, please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “**YES**”, please list which drug(s) and answer question d) i. below.

If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This is a fixed dose combination of lamivudine and raltegravir.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

If this application relies only on non product-specific published literature, answer "**N/A**"
If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "**N/A**"
If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS
--

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 5,905,082, 5,905,082*PED

No patents listed proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): 5,905,082, 5,905,082*PED
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): June 25, 2014, June 30, 2014 and July 3, 2014

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

APPEARS THIS WAY ON ORIGINAL

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/s/

MAMMAH S BORBOR
01/29/2015

MEMORANDUM

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

DATE: January 27, 2015

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

FROM: John A. Kadavil, Ph.D.
Team Lead (Acting)
Collaboration, Risk Evaluation and Surveillance Team
Office of Study Integrity and Surveillance

THROUGH: Charles Bonapace, Pharm.D.
Director (Acting)
Division of New Drugs
Office of Study Integrity and Surveillance

and

William H. Taylor, Ph.D.
Director (Acting)
Office of Study Integrity and Surveillance

SUBJECT: Review of EIR Covering NDA 206-510,
Lamivudine/Raltegravir FDC Tablets, 150 mg/300 mg,
Sponsored by Merck Sharp and Dohme Corporation, USA

At the request of the Division of Antiviral Products (DAVP), the Office of Study Integrity and Surveillance arranged inspections of the clinical and analytical portions of the following bioequivalence study:

Study #: 2012-2982
Protocol #: 253-00
Study Title: An evaluation of the comparative bioavailability between raltegravir/lamivudine (MK-0518B) 300 mg/150 mg FDC tablets (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., USA) and ISENTRESS 400 mg tablets (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., USA) administered with EPIVIR 150 mg tablets (ViiV Healthcare, USA) after a single-dose in healthy subjects under fasting conditions

Dates of Study Conduct: September 23, 2012 to October 19, 2012

Analytical Inspection:

The analytical portion of the study for the analysis of raltegravir (MK-0518) was conducted at Merck Sharp and Dohme, Operation Services 1, Oss, The Netherlands. However, because this site closed, all study records were transferred to Merck Research Laboratories, West Point, PA. An audit of the study records was therefore conducted at Merck Research Laboratories, West Point, PA from January 21-23, 2015 by OSIS Scientist John Kadavil.

The audit included a thorough examination of study records, as well as interviews and discussions with Merck management and staff. At the conclusion of inspection, no objectionable conditions were observed at the analytical site. No Form FDA-483 was issued.

The analytical portion of the study for the analysis of lamivudine was audited at (b) (4) by Ruben Ayala, Pharm.D. (OSIS) between (b) (4). Following the inspection of (b) (4), no significant issues were observed and no Form FDA-483 was issued. The EIR review discussing the inspectional findings was finalized in DARRTS on December 19, 2014.

Clinical Inspection:

The inspection of the clinical portion of the study was conducted by Sherri Jackson (ORA, (b) (4)) between November 17 and 21, 2014 at Pharma Medica Research Inc., Toronto, Canada. Following the inspection of Pharma Medica Research Inc., no significant issues were observed and no Form FDA-483 was issued. The EIR review discussing the inspectional findings was finalized in DARRTS on January 22, 2015.

Conclusion:

Following the above inspections, OSIS recommends that data for the clinical and analytical portions of study 2012-2982 be accepted for agency review.

John A. Kadavil, Ph.D.
CREST, OSIS

Final Classification:

Analytical

NAI: Merck Research Laboratories, West Point, PA

CC:

CDER OSIS PM TRACK

OSIS/Taylor/Dejernett

OSIS/DND/Bonapace/Dasgupta

OND/OAP/DAVP/Birnkrant/Borbor

Draft: JAK 01/26/2015

Edit: CRB 1/27/2015

OSI: BE6724; O:\BIOEQUIV\EIRCOVER\206510mer.lam.ral.doc

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE

Program ICAL SITES

FACTS: (b) (4)

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/s/

JOHN A KADAVIL
01/27/2015

WILLIAM H TAYLOR
01/27/2015

MEMORANDUM

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

DATE: January 22, 2015

TO: Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Team Lead
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

And

Charles Bonapace, Pharm.D.
Director (Acting)
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR Covering NDA 206510, Lamivudine/
Raltegravir FDC Tablets, 150/300mg Sponsored by Merck
Sharp and Dhome Corporation, USA

At the request of the Division of Antiviral Products (DAVP), the Division of New Drug Bioequivalence Evaluation (DNDBE) arranged inspections of the clinical and analytical portions of the following bioequivalence study:

Study #: P253-00 (2012-2982)

Study Title: "MK-0518B Bioequivalence Study"*
(*Bioequivalence study between Raltegravir/
Lamivudine (MK0518B) 150/300 mg FDC tablets
(Merck Sharp & Dohme Corp.,) and ISENTRESS® 400
mg tablets (Merck Sharp & Dohme
Corp.,) administered with EPIVIR® 150 mg tablets

(ViiV Healthcare, USA) in healthy subjects under fasting conditions)

Clinical Inspection:

The clinical site inspection for the above study was conducted by Sherri Jackson (ORA, (b)(4)) between November 17 and 21, 2014 at **Pharma Medica Research Inc., Toronto, Canada**. The inspection included a thorough examination of the protocol, protocol amendments, study records, informed consent forms, SOPs, IRB approvals, case report forms, and interviews/discussions with the firm's staff and management. Following the inspection of Pharma Medica Research Inc., no significant issues were observed and no Form FDA 483 was issued.

Analytical Inspections:

The analytical site inspection for (b)(4) was conducted by Ruben Ayla, Pharm.D. (OSIS) between (b)(4). Following the inspection of Inventive Health Clinique, no significant issues were observed and no Form FDA 483 was issued. The EIR review discussing the inspectional findings was finalized in DARRTS on December 19, 2014.

The analytical site inspection for **Merck Sharp and Dhome** is ongoing. OSIS will communicate the inspectional findings to DAVP after completion of the inspection.

Recommendations:

The clinical data from the audited study, P253-00 (2012-2982) were found to be reliable. Therefore, this DND BE reviewer recommends that the clinical data from **Pharma Medica Research Inc., Toronto, Canada** be accepted for Agency review.

Gajendiran Mahadevan, Ph.D.
Division of New Drug Bioequivalence Evaluation, OSIS

Final Classification:

Clinical Site

NAI: Pharma Medica Research Inc., Toronto, Canada
FEI: 3007426827

Page 3 - NDA 206510, Lamivudine/Raltegravir FDC Tablets sponsored
by Merck Sharp and Dhome Corporation, USA

E-mail CC:

OSIS/Taylor/Haidar/Skelly/Choi/Dejernett/Fenty-Stewart/
Nkha/Johnson

OSIS/DNDBE/Bonapace/Dasgupta/Cho/Mahadevan

CDER/OND/DAVP/Birnkrant/Borbor

ORA/[REDACTED] (b) (4) /Sandhu/Jackson

Draft: GM 01/15/2015

Edit: AD 01/22/2015; CB 01/22/2015

OSI File: BE6724; O:\BE\EIRCOVER\206510.mer.lam

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Pharma Medica Research Inc., Toronto, Canada/NDA
206510_Lamivudine

FACTS: [REDACTED] (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
01/22/2015

ARINDAM DASGUPTA
01/22/2015

CHARLES R BONAPACE
01/22/2015

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

PATIENT LABELING REVIEW

Date: January 22, 2015

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Jessica Fox, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name
(established name): DUTREBIS (lamivudine and raltegravir)

Dosage Form and
Route: film-coated tablets, for oral use

Application
Type/Number: NDA 206-510

Applicant: Merck Sharp & Dohme Corp.

1 INTRODUCTION

On April 8, 2014, Merck Sharp & Dohme Corp. submitted for the Agency's review an original 505 (B) (2) New Drug Application (NDA) 206-510 for DUTREBIS (lamivudine and raltegravir) film-coated tablets. The proposed indication for DUTREBIS (lamivudine and raltegravir) film-coated tablets is for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection. The Applicant states in their cover letter that they are cross-referencing supporting non-clinical and clinical data to the Merck NDA 22-145 for raltegravir (ISENTRESS) and to the non-Merck NDA 20-564 for lamivudine (EPIVIR) on file with FDA.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on April 17, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DUTREBIS (lamivudine and raltegravir) film-coated tablets.

2 MATERIAL REVIEWED

- Draft DUTREBIS (lamivudine and raltegravir) PPI received on April 8, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 13, 2015.
- Draft DUTREBIS (lamivudine and raltegravir) PI received on April 8, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 13, 2015.
- Approved EPIVIR (lamivudine) comparator labeling dated November 18, 2011.
- Approved ISENTRESS (raltegravir) comparator labeling dated April 8, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th 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 APFont 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 collaborative 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 is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

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

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/s/

MORGAN A WALKER
01/22/2015

JESSICA M FOX
01/22/2015

SHARON R MILLS
01/22/2015

LASHAWN M GRIFFITHS
01/22/2015

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

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

Memorandum

Date: January 22, 2015

To: Mammah Borbor, Regulatory Project Manager
Division of Antiviral Products

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

Subject: **NDA 206510**
DUTREBIS (lamivudine and raltegravir) film-coated tablets

As requested in the Division of Antiviral Products' (DAVP) consult dated April 17, 2014, the Office of Prescription Drug Promotion (OPDP) has reviewed the DUTREBIS prescribing information, patient labeling, and carton/container labeling.

OPDP reviewed the proposed substantially complete version of the prescribing information received via email from DAVP on January 13, 2015, and has the following comment:

We recommend listing the warnings and precautions in decreasing order of clinical significance. Immune Reconstitution Syndrome is currently listed as the second warning. We note that the EPIVIR labeling presents several warnings prior to Immune Reconstitution Syndrome, and that the same or similar warnings are presented after Immune Reconstitution Syndrome in the DUTREBIS labeling.

OPDP reviewed the draft container labeling submitted to the EDR on December 9, 2014, and has no comments at this time.

The Division of Medical Policy Programs and OPDP will provide a single, consolidated review of the patient labeling under separate cover.

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

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/s/

JESSICA M FOX
01/22/2015

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: December 19, 2014

TO: Wayne Dehaven, Ph.D.
Director (acting)
Division of Bioequivalence I (DBI)
Office of Generic Drugs

Ethan M. Stier, Ph.D., R.Ph.
Director (acting)
Division of Bioequivalence II (DBII)
Office of Generic Drugs

Debra Birnkrant, M.D.
Director
Division of Antiviral Products (DAVP)
Office of New Drugs

FROM: Ruben C. Ayala, Pharm.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering the analytical portions of studies
submitted in support of [REDACTED] and NDA 206510
[REDACTED] NONRESPONSIVE
[REDACTED] NONRESPONSIVE

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1. Summary

The Division of Bioequivalence and GLP Compliance (DBGLPC) arranged for inspection of the analytical portions of bioequivalence studies conducted at (b) (4).

The following bioequivalence studies were audited during the inspection:

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- **Study 253-00 (2012-2982):** MK-0518B bioequivalence study [raltegravir/lamivudine 300/150 mg FDC tablet versus ISENTRESS 400 mg tablets co-administered with EPIVIR 150 mg tablets in healthy subjects under fasting conditions].

Ruben C. Ayala, a pharmacologist from DBGLPC audited study records at [REDACTED] (b) (4) from November 9-21, 2014.

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2. Overall Recommendation

After evaluating the Establishment Inspection Report (EIR) and other inspectional documents, the data from the audited studies were found to be reliable. Thus, this reviewer recommends that the data generated by [REDACTED] (b) (4) for all thirteen studies be accepted for Agency review.

NONRESPONSIVE

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5. Division of Antiviral Products

5.1. Study 253-00 (NDA 206510)

This reviewer audited study records at (b) (4) and found no objectionable conditions. Therefore, the data generated for study 253-00 are reliable.

6. Headquarters Site Classification

VAI - (b) (4)

FEI: (b) (4)

cc:

OSI/Kassim

OSI/DBGLPC/Taylor/Dejernet

OSI/DBGLPC/GLPB/Bonapace/Dasgupta/Ayala

OSI/DBGLPC/BB/Haidar/Skelly/Choi

OSI/PM/Fenty-Stewart/Nkah/Johnson

OGD/DB1/Stier/Solana-Sodeinde

OGD/DB2/Dehaven/Kreger

OND/DAVP/Birnkrant/Borbor

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Inspections/BE Program/Analytical sites/ (b) (4)

Draft: RCA 12/16/2014, 12/18/2014, 12/19/2014

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OSI FILES# (b) (4)

FACTS: (b) (4)

(b) (4)

7. Attachments

1. Form FDA 483
2. Firm's response to Form FDA 483
3. SOP ANI 240

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/s/

RUBEN C AYALA
12/19/2014

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12/19/2014

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12/19/2014
Signing for Dr. William Taylor.

**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 Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: December 17, 2014

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Division of Pharmacovigilance II

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Product Names: Isentress (raltegravir)

Subject: Serious hepatic and psychiatric events

Application Type/Number: NDA #022145, 203045, 205786

Applicant/Sponsor: Merck

OSE RCM #: 2014-1210

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EXECUTIVE SUMMARY

This review evaluates postmarketing raltegravir safety reports in response to submission of NDA 206510 (lamivudine and raltegravir fixed-dose combination) to the FDA, with emphasis on serious liver and psychiatric adverse events. In addition, the Division of Antiviral Products (DAVP) requested that DPV do an Empirica data mining run to identify any unlabeled adverse events so that necessary labeling changes could be done with this submission.

All liver adverse events were assessed as possibly related to raltegravir. However, the majority of cases were confounded by the use of concomitant medications labeled for the risk of hepatic adverse events, had concomitant hepatitis, or missing clinical information, which limited our analysis. There was no increased severity of hepatic events compared to the product label, and no deaths could be attributed to raltegravir use.

Because raltegravir is already labeled for depression, suicidal ideation and behaviors, anxiety, and paranoia, the only psychiatric events examined in this review were those considered to be serious psychosis and hallucinations, as well as an unexpected increase in suicidal ideation and completed suicide.

Based on these FAERS cases, it is difficult to assess whether raltegravir is associated with severe psychiatric events. Just over half of the patients were reported to have a previous psychiatric history and/or drug or alcohol addiction, and many reports did not provide enough data to make an assessment.

Through Empirica data mining, pancreatitis and peripheral neuropathy were identified as being potential safety signals. A consult done by DPV in 2013 concluded that a direct causal association between pancreatitis and raltegravir could not be established based on the clinical characteristics of the cases or insufficient information. Most cases of peripheral neuropathy associated with raltegravir in FAERS were excluded due to insufficient information, and the remaining cases were confounded by concomitant drugs or medical conditions associated with peripheral neuropathy.

No new serious liver or serious psychiatric adverse events were identified in this review. Despite an elevated data mining score for peripheral neuropathy, a safety signal was not identified with raltegravir.

A review of the FAERS cases reveals that the safety labeling of raltegravir is appropriate.

DPV II will continue routine pharmacovigilance of raltegravir.

1 INTRODUCTION

This review evaluates postmarketing reports of serious liver and serious psychiatric adverse events associated with raltegravir so the Division of Antiviral Products (DAVP) can make any necessary labeling changes. In addition, DAVP requested that DPV do an Empirica data mining run to see if any other unlabeled adverse events could be identified. DAVP requested this consult because NDA 206510 (lamivudine and raltegravir fixed-dose combination) was submitted to the FDA.

Isentress® (raltegravir) is approved in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks of age and older. It is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) that was approved on October 12, 2007. It was the first integrase strand transfer inhibitor approved for use in the United States.

1.1 BACKGROUND

DPV has written two FAERS reviews pertaining to hepatotoxicity and psychiatric events associated with raltegravir use. The hepatotoxicity review, completed in February 2011, assessed hepatotoxicity and recommended that the following be added to the raltegravir label under “Adverse Reactions – Postmarketing Experience”:¹

- 1) hepatic failure with or without hypersensitivity
- 2) peritonitis

A review of psychiatric events with raltegravir, completed April 2009, stated that the labeling for depression or suicidality was adequate, but recommended adding insomnia, paranoia, and anxiety to the Adverse Reactions-Postmarketing Experience section.²

1.2 REGULATORY HISTORY

Recent regulatory action based on the hepatotoxicity and psychiatric reviews are described below.

1.2.1 Liver

Based on the findings from the 2011 DPV review, the labeling was updated to include hepatic failure under Postmarketing Experience.

The risk of peritonitis was not included in the current labeling.

1.2.2 Psychiatric

Insomnia is in the labeling under Clinical Trial Experience, and based on the 2009 DPV review, anxiety and paranoia were added to the Postmarketing Experience section of the label.

1.3 PRODUCT LABELING

1.3.1 Liver

Currently the term “hepatitis” is labeled under “Less common adverse reactions” in the most recent version of the Isentress[®] label (revised April 2014). Increases in bilirubin, AST, ALT, and ALP are labeled under ADVERSE REACTIONS.

The following information regarding patients co-infected with HIV and hepatitis B or hepatitis C virus is listed under ADVERSE REACTIONS.

6.1 Clinical Trials Experience

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus

In the randomized, double-blind, placebo-controlled trials, treatment-experienced subjects (N = 114/699 or 16%) and treatment-naïve subjects (N = 34/563 or 6%) with chronic (but not acute) active hepatitis B and/or hepatitis C virus co-infection were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal (ULN). In general the safety profile of ISENTRESS in subjects with hepatitis B and/or hepatitis C virus co-infection was similar to that in subjects without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or hepatitis C virus co-infection for all treatment groups. At 96 weeks, in treatment-experienced subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 29%, 34% and 13%, respectively, of co-infected subjects treated with ISENTRESS as compared to 11%, 10% and 9% of all other subjects treated with ISENTRESS. At 240 weeks, in treatment-naïve subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 22%, 44% and 17%, respectively, of co-infected subjects treated with ISENTRESS as compared to 13%, 13% and 5% of all other subjects treated with ISENTRESS.

6.2 Postmarketing Experience

Hepatobiliary Disorders: hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications

1.3.2 Psychiatric

Depression and suicidality were identified in clinical trials, especially in patients with a pre-existing psychiatric history. Paranoia and anxiety were identified as signals in the 2009 DPV review and were included under Postmarketing Experience.

6.1 Clinical Trials Experience

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Studies

The following ADRs occurred in <2% of treatment-naïve or treatment-experienced subjects receiving ISENTRESS in a combination regimen. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or placebo, or investigator's assessment of potential causal relationship.

Psychiatric Disorders: depression (particularly in subjects with a pre-existing history of psychiatric illness), including suicidal ideation and behaviors

6.2 Postmarketing Experience

2 METHODS AND MATERIALS

2.1 CASE DEFINITION FOR SERIOUS LIVER EVENTS

The FAERS database was searched to identify all serious liver adverse event cases associated with raltegravir. In order to be included in the analysis, the following criteria³ were required:

Temporal relationship with raltegravir use and onset of liver injury

AND

Documented liver event:

Serum ALT or AST >5x ULN *or* AlkPhos >2x ULN

OR

[Serum total bilirubin >2.5 mg/dL *or* INR >1.5] *and* elevated AST, ALT, or AlkPhos

OR

Healthcare provider (HCP)-reported liver injury (e.g., liver failure, hepatotoxicity, etc.) ± reported symptoms

If laboratory data is available, then cases are further classified by liver injury severity using the following index³:

- Score 1 (mild): Patient has elevation in ALT and/or AlkPhos but total serum bilirubin is <2.5 mg/dL and INR is <1.5
- Score 2 (moderate): Patient has elevation in ALT and/or AlkPhos and total serum bilirubin is ≥2.5 mg/dL or INR is ≥1.5
- Score 3 (moderate-severe): Patient has elevation in ALT, AlkPhos, bilirubin, and/or INR and patient is hospitalized or an ongoing hospitalization is prolonged because of DILI
- Score 4 (severe): Patient has elevation in ALT and/or AlkPhos and total serum bilirubin ≥2.5 mg/dL and there is at least one of the following: (i) hepatic failure-INR ≥ 1.5, ascites or encephalopathy; (ii) other organ failure believed to be due to DILI event
- Score 5 (fatal): Patient dies or undergoes liver transplantation because of DILI event

Causality assessment scoring, using the World Health Organization – Uppsala Monitoring Centre (WHO-UMC) system, was applied to all cases (Table 1).

Categorization	Criteria
Probable	<ul style="list-style-type: none">• Time of administration related to onset of events• Event is unlikely attributed to disease, other drugs, or radiation• Absence of other alternative explanations reported
Possible	<ul style="list-style-type: none">• Time of administration related to onset of events• Event may also be explained by disease, other drugs, or radiation• Dechallenge information was unclear or was not provided

Unlikely*	<ul style="list-style-type: none"> • Cases are not temporally related to the drug • Other medications or underlying disease provide a more likely explanation
Unassessable*	<ul style="list-style-type: none"> • Cases cannot be judged because information is insufficient or contradictory and the data cannot be supplemented or verified

*Excluded from further analysis in this case series

2.2 FAERS SEARCH STRATEGY

2.2.1 Serious Liver Events

The FAERS database was searched with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	September 10, 2014
Time period of search	October 19, 2010 [†] - September 10, 2014
Search type	Quick Query
Product Terms	Product names: raltegravir, raltegravir potassium, Isentress Product active ingredient: raltegravir, raltegravir potassium
MedDRA Search Terms (Version 17.0)	HLT: Hepatic failure and associated disorders PTs: Hepatic fibrosis, Hepatic necrosis, Liver transplant, Hepatitis fulminant, Liver and small intestine transplant, Renal and liver transplant, Hepatitis acute
* See Appendix A for a description of the FAERS database.	
[†] Last search date of previous review	

A Clinical Specialty Network (CSN) Query was performed with the strategy described in Table 3.

Table 3. CSN Search Strategy*	
Date of search	September 10, 2014
Time period of search	October 19, 2010 [†] - September 10, 2014
Search type	Ad hoc query “Quick Query with Patient ID prompts”
Product Terms	Product active ingredient: raltegravir, raltegravir potassium
Other Search Criteria	Patient ID: %DILIN% Patient ID2: %ALFSG%
* See Appendix A for a description of the CSN	
[†] Last search date of previous review	

2.2.1 Serious Psychiatric Events

The FAERS database was searched with the strategy described in Table 4.

Table 4. FAERS Search Strategy*	
Date of search	August 25, 2014
Time period of search	February 4, 2009 [†] - August 25, 2014
Product Terms	Raltegravir, raltegravir potassium, Isentress
MedDRA Search Terms (Version 17.0)	PTs: Depression suicidal, acute psychosis, psychotic behavior, psychotic disorder, completed suicide, suicidal behavior, suicidal ideation, suicide attempt, hallucination, hallucination auditory, hallucination gustatory, hallucination olfactory, hallucination synaesthetic, hallucination tactile, hallucination visual, hallucinations mixed, schizoaffective disorder bipolar type
* See Appendix A for a description of the FAERS database.	
[†] Last search date of previous review	

2.3 DATA MINING SEARCH STRATEGY

The Empirica Signal database was searched with the strategy described in Table 5.

Table 5. Data Mining Search Strategy*	
Data Refresh Date	August 27, 2012
Product Terms	Raltegravir, Isentress
Empirica Signal Run Name	Generic (S) by PT or SMQ
Search Date	September 16, 2014
MedDRA Search Strategy	All terms
* See Appendix A for description of Data Mining of FAERS using Empirica Signal.	

3 RESULTS

3.1 SERIOUS LIVER EVENTS

3.1.1 FAERS Case Selection

The FAERS search retrieved 33 reports. After applying the case definition in Section 2 and accounting for duplicate reports, 8 cases were included in the case series of serious liver adverse events reported with raltegravir use (see Figure A).

Figure A. FAERS Case Selection

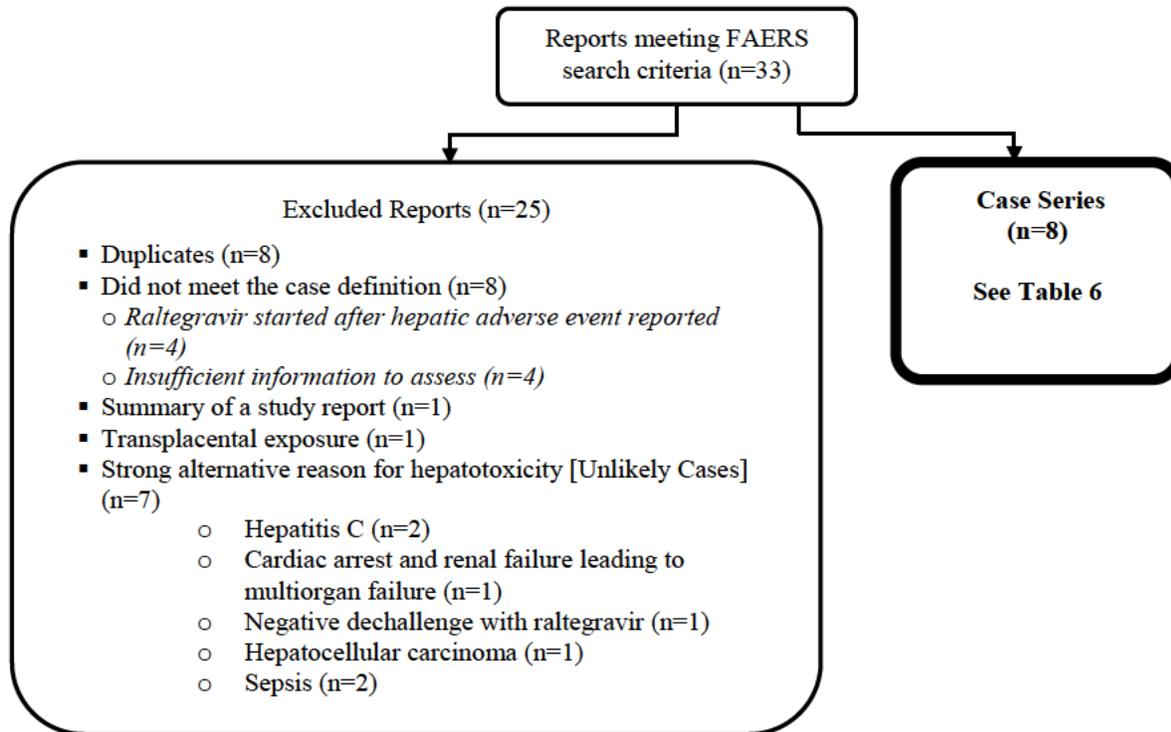


Table 6 summarizes the 8 FAERS cases of serious liver adverse events reported with raltegravir for this case series.

Appendix B lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 8 cases in this case series.

Table 6. Descriptive characteristics of serious liver adverse event cases reported with raltegravir use, received by FDA from October 19, 2010[†] to September 10, 2014 (N=8)	
Age (Years) (N=7)	Mean 49.6 Median 49 Range 31-64
Gender	Male 4 Female 4
Country of Reporter	Foreign 7 United States 1
Report Type	Expedited 8 Direct 0
Liver Adverse Event	Hepatic Failure 5 Acute Hepatitis 2

	Regenerative Nodular Hyperplasia 1
Duration between first raltegravir dose and liver symptoms (days) (N=7)	Mean 128.14 Median 87 Range 20-378
Concomitant hepatotoxic medications (more than 1 reported per case)	Darunavir 2 Etravirine 2 Ritonavir 2 Amoxicillin 1 Didanosine 1 Emtricitabine/tenofovir 1 Isoniazid 1 Lopinavir/ritonavir 1 Maraviroc 1 Rifampin 1 Tenofovir 1
Viral Hepatitis Co-infection	HBV 1 HCV 2 HBV/HCV 1 None reported 4
Hypersensitivity (rash) component	Yes 3 None reported 5
Antiretroviral treatment discontinuation	Yes 5 No 1 Unknown 2
Liver injury severity based on case definition index	Score 4 (severe) 2 Laboratory data not available 6
Primary Serious Outcome*	Death 3 Life-Threatening 1 Hospitalization 4
Clinical Outcome	Death 3 Recovered/Recovering 5
Causality	Possible 8 Probable 0
† Last search date of previous review *Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.	

As shown in Table 6, there appears to be a possible temporal relationship between the start of raltegravir therapy and liver-related AEs. However, the majority of cases were confounded by the use of concomitant medications labeled for the risk of hepatic adverse events, had preexisting hepatitis, or insufficient information. There was no increased severity of labeled hepatic events and none of the three deaths could be attributed to raltegravir use. A representative case is described below, and a summary of all eight hepatotoxicity cases can be found in Section 8.3, Appendix C.

- Case# 7867675 (FDA received date 2011, France, Outcomes: HO)** describes a 48-year-old female patient who received raltegravir, maraviroc, etravirine for 87 days. Baseline laboratory values include AST 75 IU/L (normal range: 15-37 IU/L) and ALT 75 IU/L (normal range: 12-78 IU/L). The patient presented with vomiting, abdominal pain, jaundice, and no rash. On admission, laboratory values included AST 952 IU/L and ALT 1153 IU/L. Antiretroviral regimen was discontinued and abdominal ultrasound confirmed acute hepatitis. The patient's medical history included co-infection with HCV (not treated) and HBV (treated), pneumocystis, hysterectomy, and previous episode of drug-induced hepatitis while treated with nevirapine. At the time of the report, the patient was improving and the reporting physician assessed the causality between antiretrovirals and adverse events as possible. *Reviewer's comments: Causality assessed as possible because the case is confounded by concomitant use of maraviroc which is labeled for the risk of hepatitis under WARNINGS AND PRECAUTIONS and etravirine which is labeled for hepatic failure and hepatitis under "Less Common Adverse Reactions."*

3.1.2 Clinical Specialty Network (CSN) Case Selection

The FAERS search retrieved 1 report. After applying the case definition in Section 2, the case was excluded because it provided a strong alternative reason for hepatotoxicity (i.e., sepsis).

3.2 SERIOUS PSYCHIATRIC EVENTS

The FAERS search retrieved 68 reports. After accounting for duplicate reports and exclusions, 43 cases were included in the case series of serious psychiatric adverse events reported with raltegravir use (see Figure B).

Figure B. FAERS Case Selection

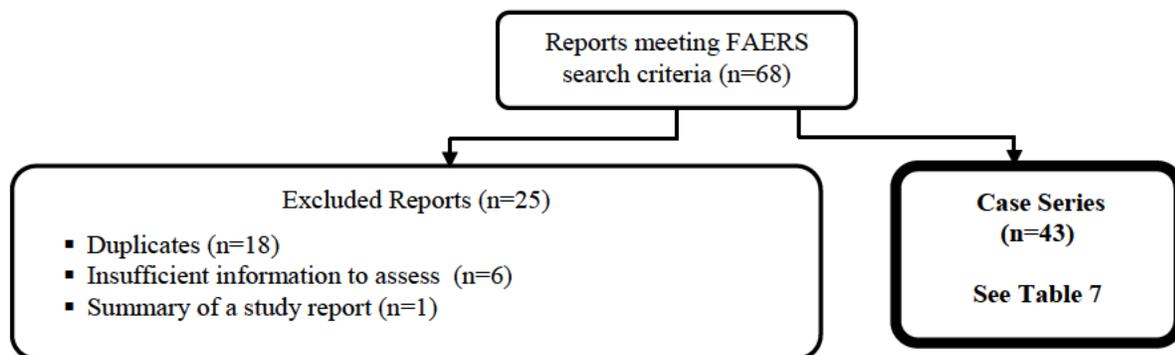


Table 7 summarizes the 43 FAERS cases of serious psychiatric adverse events reported with raltegravir for this case series.

Appendix B lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 43 cases in this case series.

Table 7. Descriptive characteristics of serious psychiatric events reported with raltegravir use, received by FDA from February 4, 2009[†] to August 25, 2014 (N=43)	
Age (n=40)	Mean: 44.6 years Median: 45 years Range: 17-79 years
Gender	Male: 36 Female: 6 Not reported: 1
Country of Reporter	United States: 22 Foreign: 21
Report Type	Expedited: 42 Direct: 1
Primary Serious Outcome*	Death: 6 (14%) Life-Threatening: 10 (23%) Hospitalization: 8 (19%) Other: 15 (35%) Not reported: 4 (9%)
Serious Psychiatric Adverse Event ^{††}	Completed suicide: 4 (9%) Suicide attempt: 10 (23%) Suicidal ideation: 17 (40%) Depression suicidal: 1 (2%) Psychotic disorder: 7 (16%) Hallucination: 5 (12%) Hallucination auditory: 3 (7%) Hallucination visual: 1 (2%)
Previous psychiatric history and/or drug or alcohol addiction	Yes: 23 (53%) No: 3 (7%) Not reported: 17 (40%)
Time to onset from first raltegravir dose and serious psychiatric symptoms (n=32)	Mean: 253.4 days Median: 100 days Range: 2 days - 3 years
Raltegravir stopped, events improved	n=8 (positive dechallenge)
Raltegravir stopped, events not improved	n=1 (negative dechallenge)
Raltegravir continued, events improved	n=2
Raltegravir continued, events not improved	n=2
[†] Last search date of previous review *Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. ^{††} Patient may have experienced more than one adverse event in this list.	

Table 7 identifies a total of six deaths, four of which were completed suicide. A wide range was found from the start of raltegravir use to the onset of serious psychiatric symptoms (range, 2 days

to 3 years). Of note, 53% of the patients in this case series had a previous psychiatric history and/or drug or alcohol addiction.

3.2.1 Deaths (n=6)

There were six deaths in this case series (Cases #6904866; 8718206; 9006294; 9284556; 9385931; 8201355, 8226397, 9204855). Four of the deaths were due to completed suicide, and two were related to medical complications.

One of the medical deaths (**#6904866, FDA receive date 2009, Spain**) was a patient who was hospitalized with severe COPD and cor pulmonale, developed anxiety and worsening of his already diagnosed psychotic disorder three days after starting raltegravir. The patient died suddenly four days after raltegravir was stopped. The second medical death (**#8718206, FDA receive date 2012, France**) was in a patient who developed lactic acidosis while taking didanosine and tenofovir. Didanosine and tenofovir were stopped and raltegravir and etravirine were started. Eleven days later the patient had visual hallucinations as well as acute renal failure; the patient went into cardiac arrest and died.

Three of the suicide cases (**#9006294; 9284556; 9385931**) were very brief and had insufficient details to assess causality. Duration of raltegravir to onset of suicide was available in only one patient (835 days).

The last case (**#8201335, 8226397, 9204855; FDA receive date 2011, Switzerland**) was a 48-year old male who commenced efavirenz/ emtricitabine/tenofovir DF on 04 August 2011. One day after commencing efavirenz/emtricitabine/tenofovir DF the patient experienced severe anxiety, insomnia, nightmares and a depressive state of sudden onset. The patient was noted not to have had any prior history of depression, psychiatric illness or sleep disturbance in the past or before commencing efavirenz/ emtricitabine/tenofovir DF. Bactrim DS was the only concomitant medication documented in the report. On 10 August 2011 treatment with efavirenz/emtricitabine/tenofovir DF was discontinued due to the events, which were considered to be efavirenz related side effects by the reporter. The patient presented at the ED on (b) (6) for his depressive state, sleeplessness and anxiety. On (b) (6) the patient's efavirenz plasma level was 350ng/mL, 5 days after discontinuing efavirenz/emtricitabine/tenofovir DF. On (b) (6) the patient was treated for depressive state and insomnia with Benocten/Benadryl with no effect, and Alprazolam, which worked occasionally. On (b) (6) the patient was treated for depressive state and insomnia with Zolpidem, with no effect, and on (b) (6) was treated for depressive state and insomnia with Trazodone, which also had no effect. The patient was referred to a psychiatrist and spent the night of (b) (6) under surveillance in the psychiatry unit. On (b) (6) the patient started treatment with Truvada and Isentress, however the symptoms did not improve and at a control visit on (b) (6) the patient reported to be still experiencing anxiety and insomnia, albeit a little less. On (b) (6) treatment with emtricitabine/tenofovir DF and Isentress was discontinued. On (b) (6) the patient began experiencing paranoia and nightmares. On (b) (6) the patient was treated for depressive state and insomnia with mirtazapine. On (b) (6) the patient died after committing suicide by hanging. *Reviewer's comments: Five days after*

stopping Atripla, the patient's reported efavirenz plasma level was elevated at 350ng/mL. This is slightly lower than steady state plasma levels (410 ng/mL), which are usually reached in 6-10 days. Because efavirenz is labeled for neuropsychiatric events and the drug appeared to have a slow elimination rate, efavirenz could be a confounding factor. However, this patient, with no psychiatric history, was off efavirenz for almost 2 months before his suicide. The patient had more recently been taking raltegravir for 20 days, and was off for 2 weeks before his suicide. Causality assessed as possible.

3.2.2 Time to Onset

The time from the first dose of raltegravir to the onset of psychiatric symptoms ranged widely from 2 days to 3 years (with a mean of 253.4 days and a median of 100 days; n=32). To see if serious psychiatric events occurred more frequently or were more severe when raltegravir was started more recently, cases with an onset of 30 days or less were compared with cases with an onset of greater than 6 months.

Table 8. Descriptive characteristics of serious psychiatric events reported with raltegravir use, received by FDA from February 4, 2009[†] to August 25, 2014		
Time to first onset of symptoms	30 days or less (n=14)	Greater than 6 months (n=11)
Primary serious outcome*		
Death	3 ^{††} (21%)	1 (9%)
Life-Threatening	2 (14%)	3 (27%)
Hospitalization	3 (21%)	0
Other	6 (43%)	5 (45%)
Not reported	0	2 (18%)
Serious psychiatric adverse event**		
Completed suicide	1 (7%)	1 (9%)
Suicide attempt	3 (21%)	3 (27%)
Suicidal ideation	3 (21%)	5 (45%)
Psychotic disorder	2 (14%)	0
Hallucination	3 (21%)	2 (18%)
Hallucination auditory	1 (7%)	0
Hallucination visual	1 (7%)	0
Previous psychiatric history and/or drug or alcohol addiction		
Yes	9 (64%)	5 (45%)
No	1 (7%)	2 (18%)
Not reported	4 (29%)	4 (36%)
Time to onset from first raltegravir dose and serious psychiatric symptoms		
Mean	13.8 days	641.7 days
Range	2 – 30 days	6.2 months – 3.2 years

†Last search date of previous review
 *Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
 ††Only one patient (7%) completed suicide; the other two deaths were medically related
 **Patient may have experienced more than one adverse event in this list.

Table 8 shows that there were minimal differences in the outcomes or the particular serious adverse events between the two groups. There were a higher percentage of cases with a previous psychiatric and/or addiction history in patients taking raltegravir for 30 days or less; however, the number of cases in each group is very small making it hard to determine whether the difference is real.

3.3 DATA MINING

A data mining run was done and the top PT terms with an EB05 of greater than 2 were reviewed. All of the terms, with the exception of pancreatitis and peripheral neuropathy (see Table 9), were either labeled or related to disease progression. The complete data mining list can be found in Section 8.4, Appendix D.

Table 9: Data Mining Run Raltegravir and Unlabeled PT Terms

PT Frequency Ranking	Generic Name	PT or SMQ	N	EB05
89	Raltegravir	Acute pancreatitis (SMQ) [algorithm]	50	2.468
100	Raltegravir	Acute pancreatitis (SMQ) [narrow]	41	2.273
101	Raltegravir	Neuropathy peripheral	26	2.242
102	Raltegravir	Pancreatitis acute	14	2.241

3.3.1 Pancreatitis

A consult that evaluated cases of pancreatitis associated with raltegravir use was completed by DPV on June 24, 2013.⁶ The review concluded that a direct causal association between pancreatitis and raltegravir could not be established in the 42 cases identified in the FAERS database since approval. Increases in serum pancreatic amylase and serum lipase are labeled under Adverse Reactions-Clinical Trials Experience, although pancreatitis is not labeled. The current labeling is considered to be adequate.

3.3.2 Peripheral Neuropathy

The FAERS database was searched with the strategy described in Table 10.

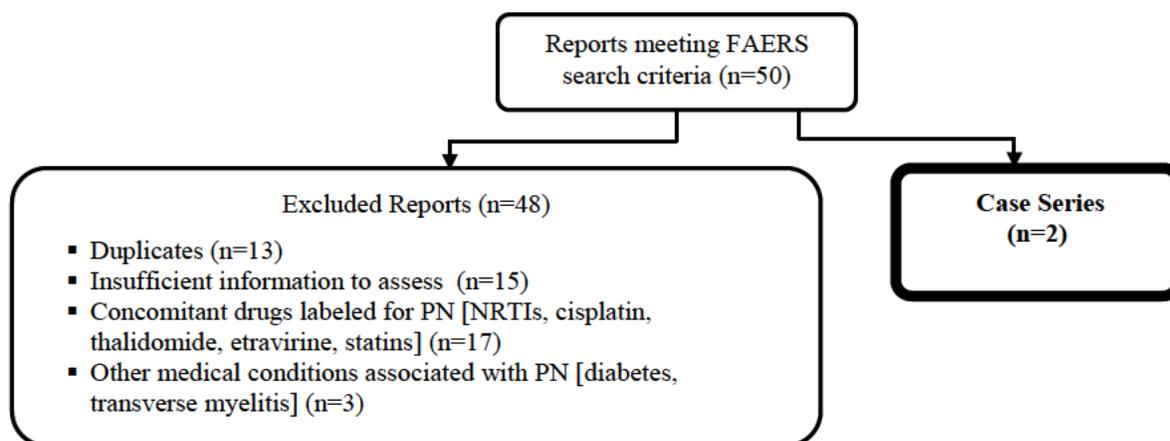
Table 10. FAERS Search Strategy*	
Date of search	October 15, 2014
Time period of search	January 1, 1969 - October 15, 2014

Product Terms	Raltegravir, raltegravir potassium, Isentress
MedDRA Search Terms (Version 17.0)	PT: Neuropathy peripheral
* See Appendix A for a description of the FAERS database.	

3.3.2.1 FAERS Case Selection

The FAERS search retrieved 50 reports. After accounting for duplicate reports and exclusions, 2 cases were included in the case series of peripheral neuropathy (PN) reported with raltegravir use (see Figure C).

Figure C. FAERS Case Selection



The two cases are summarized below:

1. **#6542414 (FDA receive date 2008, Australia, Outcome: OT):** This spontaneous report from a physician concerns a 55-year old male patient from Australia. The patient's medical history and concurrent conditions included: HIV and peripheral neuropathy (acutely symptomatic in the hands and feet). The patient was treated with darunavir, initiated on an unknown date for HIV. Non-company suspect interacting drugs included: MK-0518 (raltegravir) for HIV. Concomitant medications were not reported. On an unknown date, the patient experienced drug interaction with raltegravir and peripheral neuropathy. The doctor reported that the combination of MK-0518 and darunavir may have contributed to this event but did not attribute the event to darunavir alone. The patient had been on darunavir for 2 months. The patient outcome was unknown for peripheral neuropathy and drug interaction with raltegravir. *Reviewer's comments: Causality assessed as possible although the analysis is limited because the report provided limited information.*
2. **8713061 (unknown age and sex, Italy):** This report was received from literature article.⁸ A patient of unspecified age and sex had a medical history of hemophilia A, HIV, hepatitis B and C infection which caused liver disease. The patient experienced

antiretroviral multidrug resistance, and was currently being treated with darunavir, raltegravir, and ritonavir. No concomitant medications were reported. On an unspecified date, 23 months after raltegravir initiation, the patient experienced peripheral neuropathy. The patient was continued with the regimen of raltegravir, darunavir and ritonavir. The outcome of the event peripheral neuropathy was not reported. It was reported that the physician deemed the association with raltegravir as possible, as it was impossible to exclude that the neuropathy might be associated with one of the other antiretroviral drugs given. *Reviewer's comments: Causality assessed as possible although the analysis is limited because the report provided limited information.*

4 DISCUSSION

The focus of this review is to evaluate cases of serious liver and serious psychiatric adverse events with the use of raltegravir. An Empirica data mining run was also done to identify any unlabeled potential signals.

This review identified 8 FAERS cases associated with serious liver events. The median drug exposure time to event onset was 87 days, with a range of 20 – 378 days, which supports a temporal association. Most idiosyncratic DILI events occur between 5 and 90 days after starting the suspect drug, but cases outside of this window can occur.⁷ In a majority of the FAERS cases, serious liver events led to discontinuation of antiretroviral therapy. Four patients reported viral hepatitis co-infection, and the risk of liver function abnormalities is increased in this patient population. There was one case that reported a rechallenge with raltegravir after the patient received a liver transplant, but the outcome of the rechallenge is unknown. Three cases reported a fatal outcome with raltegravir; the fatal outcomes were due to hepatic failure in combination with renal failure, sepsis, and cholestatic hepatitis, and could not be reasonably attributed to raltegravir.

All liver adverse events were assessed as possibly related to raltegravir. The majority of cases were confounded by the use of concomitant medications labeled for the risk of hepatic adverse events (i.e., maraviroc, etravirine, didanosine, darunavir, tenofovir, ritonavir, isoniazid, rifampin, amoxicillin, lopinavir/ritonavir, emtricitabine/tenofovir). In addition, some cases had missing clinical information (i.e., laboratory data and clinical course unknown, concomitant medications unknown, medical history unknown) which limited our analysis. There was no increased severity of labeled hepatic events and no deaths could be attributed to raltegravir use.

Because raltegravir is already labeled for depression, suicidal ideation and behaviors, anxiety, and paranoia, the only psychiatric events examined in this review were those considered to be serious psychosis and hallucinations, as well as an unexpected increase in suicidal ideation and completed suicide.

Based on these FAERS cases, it is difficult to assess whether raltegravir is associated with severe psychiatric events. Just over half of the patients were reported to have a previous psychiatric history and/or drug or alcohol addiction, and many reports did not provide enough data to make an assessment. Of the four completed suicide reports in this cases series, three had insufficient information. In the fourth case, the patient had been treated with efavirenz, which has known

neuropsychiatric adverse events, the month before his death. The patient became depressed almost immediately after taking efavirenz and his serum levels of efavirenz remained elevated after discontinuation. Raltegravir was then started; however, the patient committed suicide a month later.

The time from the first dose of raltegravir to the onset of psychiatric symptoms ranged widely from 2 days to 3 years (with a mean of 253.4 days). Because of prolonged duration of therapy with raltegravir in many cases, it was difficult to assess whether there was a temporal relationship with serious psychiatric events and the drug. Cases with an onset of symptoms of 30 days or less were compared with an onset of greater than six months, and there was minimal difference in the outcome or the particular serious adverse event between the two time periods. There were a higher percentage of cases with a previous psychiatric and/or addiction history in patients taking raltegravir for 30 days or less; however, the number of cases in each group is very small making it hard to determine whether there is a real difference (30 days or less: n=9 [64%] vs. greater than 6 months: n=5 [45%]).

Through data mining, pancreatitis and peripheral neuropathy were identified as potential safety signals. A consult done by DPV in 2013 concluded that a direct causal association between pancreatitis and raltegravir could not be established based on the clinical characteristics of the cases or insufficient information.

A search of FAERS for cases of peripheral neuropathy associated with raltegravir retrieved 50 reports; however, most were excluded due to insufficient information, confounding by concomitant drugs or medical conditions associated with peripheral neuropathy. Of the two remaining cases, raltegravir could have possibly been related, but the outcome of the peripheral neuropathy was not reported, making an assessment difficult.

5 CONCLUSION

No new serious liver or serious psychiatric adverse events were identified in this review. Despite an elevated data mining score for peripheral neuropathy, a safety signal was not identified with raltegravir.

A review of the FAERS cases reveals that the safety labeling of raltegravir is appropriate.

6 RECOMMENDATIONS

DPV II will continue routine pharmacovigilance of raltegravir.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

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

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

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

Clinical Specialty Networks (CSN)

Clinical Specialty Networks are external networks that enroll patients and collect detailed clinical information under a study protocol and/or surveillance system; they ideally have a Case Report Form (CRF), and are typically in the academic environment. CSN have a primary focus: a) Disease State (e.g., Acute Liver Failure), or b) Drug-induced diseases (e.g., Drug Induced Liver Injury Network). These groups are not formally doing pharmacovigilance, but are instead trying to advance their science, and collect detailed information and recruit patients to expand their dataset. They happen to have expert reports (whether in total or a subset of their data) that involve drug-induced safety issues. The current role of CSNs in OSE/OPE/DPV is:

- Complement FAERS data.
- Strengthen signal evaluation: stratify by CSN and non-CSN reports.
- Potential to aid in signal detection

Two CSNs, both reporting liver injury cases, are available in the FAERS- the Drug-induced Liver Injury Network (DILIN) and the Acute Liver Failure Study Group (ALFSG). These networks are briefly defined below, with additional comparison in Table 1.

- DILIN: Established to advance understanding and research into DILI by initiating a prospective registry of patients with bona fide DILI for future studies of host clinical, genetic, environmental and immunological risk factors. DILIN is the first CSN with data in FAERS since 2005.
- ALFSG: Examine prospectively the epidemiology and outcomes of all forms of ALF in the United States at participating study centers. Newest CSN with data in FAERS since 2010.

Table 1. Current DILI Clinical Specialty Networks reporting to FAERS

<u>DILIN</u> (Drug-induced Liver Injury Network)		<u>ALFSG</u> (Acute Liver Failure Study Group)
NIDDK*	Funding	NIDDK* and FDA (pilot funding)
2003	Enrollment Origination	1998
>1000	Subjects Enrolled	217 (Non-APAP)
2005	FAERS Origination	2010
>800 [^]	FAERS Cases	~200 [^]
>2 y/o	Subject Age	>18 y/o
8 (was 5)	Participating Sites	13 (was 22)
No	APAP Inclusion	Yes (APAP cases not reported to FAERS)
ALT/AST 5x ULN on two occasions OR AP 2x ULN on two occasions OR TB >2.5mg/dl + elevated AST, ALT, or AP OR INR >1.5 + elevated AST, ALT, or AP	Inclusion Criteria (Within 6 months of illness onset)	Coagulopathy (INR ≥1.5) AND Encephalopathy

*National Institute of Diabetes and Digestive and Kidney Diseases

[^]As of August 2013

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then

quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

8.2.1 *Serious Liver Events (n=8)*

	FAERS Case#	Manufacturer Control#
1	7867675	(b) (4)
2	7959187	
3	7973954	
4	8153486	
5	8154430	
6	8772035	
7	9405564	
8	9666127	

8.2.2 *Serious Psychiatric Events (n=43)*

	FAERS Case#	Manufacturer Control#
1	10036404	(b) (4)
2	10278369	
3	10307375 10314332	
4	6622369	
5	6753908 7039627 7462084 7629765 9691405	
6	6893650	
7	6997878	
8	7010034 7625386	
9	7272585	

10	7387312	(b) (4)
11	7397949	
12	7551406 9457834	
13	7625373	
14	7829395	
15	7895568	
16	8068001	
17	8102434	
18	8161107	
19	8201335 8226397 9204855	
20	8318294 8321475	
21	8663465	
22	8722402	
23	9006294	
24	9102786 9128131	
25	9146412 9161140	
26	9284556	
27	9308966	
28	9385931	
29	9447631 9448542 9629572	
30	9575882	
31	9649382	
32	6904866	
33	6985556	
34	7631072	
35	7666126 8795438	
36	7748545	
37	7893638 7895572 7950684 8781511	
38	7894254	
39	7987616	
40	8238475	
41	8718206	
42	9358922	
43	9768361	

8.2.3 Peripheral Neuropathy Cases (n=2)

	FAERS Case#	Manufacturer Control#
1	6542414	(b) (4)
2	8713061	(b) (4)

8.3 APPENDIX C. SUMMARY OF EIGHT CASES OF SERIOUS LIVER ADVERSE EVENTS REPORTED WITH RALTEGRAVIR USE

1. Case# 7867675 (FDA received date 2011, France, Outcomes: HO) describes a 48-year-old female patient who received raltegravir, maraviroc, etravirine for 87 days. Baseline laboratory values include AST 75 IU/L (normal range: 15-37 IU/L) and ALT 75 IU/L (normal range: 12-78 IU/L). The patient presented with vomiting, abdominal pain, jaundice, and no rash. On admission, laboratory values included AST 952 IU/L and ALT 1153 IU/L. Antiretroviral regimen was discontinued and abdominal ultrasound confirmed acute hepatitis. The patient's medical history included co-infection with HCV (not treated) and HBV (treated), pneumocystosis, hysterectomy, and previous episode of drug-induced hepatitis while treated with nevirapine. At the time of the report, the patient was improving and the reporting physician assessed the causality between antiretrovirals and adverse events as possible. Reviewer's comments: Causality assessed as possible because the case is confounded by concomitant use of maraviroc which is labeled for the risk of hepatitis under WARNINGS AND PRECAUTIONS and etravirine which is labeled for hepatic failure and hepatitis under "Less Common Adverse Reactions".
2. Case# 7959187 (FDA received date 2011, France, Outcomes: HO, OT) describes a 49-year-old male patient who developed portal hypertension and hepatic cytolysis based on abdominal ultrasound after 378 days of therapy with raltegravir. Concomitant medications included ritonavir, atazanavir, and tenofovir. The patient was diagnosed with HIV in 1998 and had been on various antiretroviral therapies, including didanosine for seven years which was replaced with raltegravir. A liver biopsy noted portal fibrosis without any cirrhosis and a month later, a regenerative nodular hyperplasia (i.e., noncirrhotic portal hypertension) diagnosis was confirmed. At the time of the report, the patient had not yet recovered. According to the narrative, the reporter did not think the adverse events were related to raltegravir therapy. No laboratory values were provided. Reviewer's comments: Causality assessed as possible because the case is confounded by long-term use of didanosine prior to initiation of raltegravir. There have been reports of patients with HIV infection who develop noncirrhotic portal hypertension^{4,5}. The pathogenesis is thought to be related to the effect of HAART (particularly long-term exposure to didanosine) on the microvasculature of the liver or the direct effect of the HIV itself. Regenerative nodular hyperplasia has a time to onset of 1-6 years which fits the time frame described in this case. Of note, raltegravir and the concomitantly administered antiretrovirals are labeled for various hepatic adverse events including

hepatitis, transaminase elevations, and hyperbilirubinemia but they are not labeled for regenerative nodular hyperplasia.

3. Case# 7973954 (FDA received date 2011, Switzerland, Outcomes: HO, OT) describes a 31-year-old male patient who experienced drug reaction with eosinophilia and systemic symptoms (DRESS) and hepatic failure after 122 days of treatment with raltegravir, etravirine, and darunavir. Antiretroviral treatment was withdrawn and the patient recovered on an unknown date. The reporting physician considered the events to be “certainly related” to etravirine and darunavir. Reviewer’s comments: Causality assessed as possible due to confounding concomitant medications and limited clinical information. Etravirine is labeled for the risk of severe skin and hypersensitivity reactions including DRESS and hepatic failure under WARNINGS AND PRECAUTIONS while darunavir and raltegravir are labeled for the risk of severe skin reactions under WARNINGS AND PRECAUTIONS but DRESS is unlabeled. Although raltegravir’s contribution to the events can’t be ruled out, the confounding concomitant medications and limited clinical information limits our analysis (i.e., laboratory data and clinical course unknown, concomitant medications unknown, medical history unknown).
4. Case# 8153486 (FDA received date 2011, United States, Outcomes: DE, HO, OT) describes a 43-year-old female HCV co-infected patient who developed “diffuse, scaly rash with no mucosal lesions covering her whole body”, renal failure, hypotension, and increased bilirubin and liver transaminases (i.e., ALT 199 IU/L, AST 363 IU/L, AlkPhos 322 IU/L, bilirubin 9.9 mg/dL) after 20 days of treatment with raltegravir, darunavir, ritonavir, lamivudine, and abacavir. The patient was enrolled in study “TMC114HIV3014: The Optimized Treatment that Includes or Omits NRTIs (OPTIONS) Trial”. She was admitted to the intensive care unit with a diagnosis of septic shock and acute renal failure. Antiretroviral regimen was discontinued and the patient was treated with intravenous fluids, vancomycin, piperacillin/tazobactam, rifaximin, and lactulose. During the hospitalization, the patient's rash improved but she developed fulminant hepatic failure reported as Grade 4 (i.e., ALT 194 IU/L, AST 268 IU/L, AlkPhos 207 IU/L, bilirubin 29.9 mg/dL). She was started on hemodialysis for renal failure. She developed E. Coli urosepsis and died while in the hospital. The case narrative states that the events were likely a systemic drug reaction to abacavir, raltegravir, or darunavir. Of note, the patient had a previous episode of acute renal failure in the setting of drug abuse (i.e., benzodiazepines, cocaine, opiates) 97 days prior to the current event while receiving treatment with raltegravir, darunavir, etravirine, emtricitabine/tenofovir, and ritonavir. Reviewer’s comments: Causality assessed as possible due to confounding concomitant medications. The patient’s liver injury qualifies as Score 4 (severe) according to the case definition. Concomitant medications are labeled for both skin reactions (darunavir is labeled for the risk of severe skin reactions under WARNINGS AND PRECAUTIONS, lamivudine is labeled for skin rash under ADVERSE REACTIONS, abacavir is labeled for hypersensitivity reactions including rash under WARNINGS AND PRECAUTIONS, and SJS and TEN under “Post-Marketing Experience”) and hepatic adverse events (i.e., ritonavir is labeled for the risk of drug-induced hepatitis under WARNINGS AND PRECAUTIONS and liver injury including some fatalities under “Post-Marketing Experience”). Additionally, the risk of liver function abnormalities is increased in patients with pre-existing liver dysfunction, such as

HCV. Raltegravir is labeled for the risk of severe skin reactions under WARNINGS AND PRECAUTIONS and the risk of hepatitis under “Less Common Adverse Reactions”.

5. Case# 8154430 (FDA received date 2011, France, Outcomes: DE, HO, LT, OT) describes a 57-year-old male patient who experienced acute respiratory distress, acute pneumopathy and cutaneous-mucous icterus and moderate ascites without signs of hepatic encephalitis five days after being discharged after an alcoholism intoxication relapse. The duration of treatment with raltegravir is unknown and concomitant drugs included ritonavir for unknown duration and darunavir for 13 days. The patient’s medical history and baseline liver function is unknown. An abdominal ultrasound did not show liver or bile duct anomaly. The patient then experienced respiratory decompensation and hemodynamic instability requiring ventilation and vasopressors. The patient progressed to multiple septic episodes and multiorgan failure leading to death. The cause of death was reported as icterus, cholestatic hepatitis, and hepatic failure. The reporter assessed all drugs as suspect but causality was assessed as doubtful. Reviewer’s comments: Causality assessed as possible because case is confounded by alcoholism and the use of concomitant medications labeled for hepatic events. The duration of treatment with raltegravir is unknown so a temporal relationship can’t be assessed. Darunavir is the only drug recently added to the regimen of raltegravir and ritonavir and it’s labeled for the risk of acute hepatitis and hepatic enzyme increased under ADVERSE REACTIONS. Additionally, darunavir in combination with ritonavir is labeled for the risk of drug-induced hepatitis under WARNINGS AND PRECAUTIONS. Though the contribution of raltegravir to the adverse events can’t be excluded, the lack of information to assess temporal association and the use of confounding concomitant medications labeled for hepatic adverse events limits our analysis.
6. Case# 8772035 (FDA received date 2014, France, Outcomes: HO, LT, OT) describes a 55-year-old female who experienced fulminant hepatitis after 46 days of therapy with raltegravir, lamivudine, and tenofovir. The patient was concomitantly receiving tuberculosis (TB) treatment with rifampin and isoniazid for 82 days at the time of the adverse events. After 14 days of TB therapy and before initiation of antiretroviral therapy, the patient’s laboratory values included AST 37 IU/L, ALT 40 IU/L, AlkPhos 65 IU/L, and serum bilirubin 3 umol/L. After 67 days of TB therapy and 31 days of antiretroviral therapy, the patient’s laboratory values included AST 62 IU/L, ALT 39 IU/L, AlkPhos 67 IU/L, and serum bilirubin 7 umol/L. Fulminant hepatitis diagnosis was based on liver biopsy results showing massive hepatic necrosis and laboratory values with AST 2900 IU/L, ALT 1900 IU/L, AlkPhos 172 IU/L, and bilirubin 238 umol/L. The patient was placed on therapy with N-acetylcysteine and four days later underwent hepatic transplantation. Antiretroviral therapy was resumed post-transplant with emtricitabine/tenofovir and raltegravir. The reporter states that the relationship of the adverse events to the drugs could be related to antiretroviral or TB drugs. Reviewer’s comments: Causality assessed as possible because the case is confounded by the use of concomitant medications labeled for hepatic events. Patient’s liver injury qualifies as Score 4 (severe) according to the case definition. Isoniazid is labeled for the risk of severe and sometimes fatal hepatitis under WARNINGS AND PRECAUTIONS. Isoniazid-related hepatitis usually occurs during the first three months of treatment which

fits the time frame of the case. Rifampin is labeled for the risk of transient abnormalities in liver function tests and the rare risk of hepatitis under ADVERSE REACTIONS. Tenofovir is labeled for the risk of hepatitis and increased liver enzymes under “Postmarketing Experience”. A temporal association between fulminant hepatitis and both antiretroviral and TB therapy exists which limits our ability to identify the culprit for the adverse event.

7. Case# 9405564 (FDA received date 2013, Great Britain, Outcomes: DE, HO, OT) describes an HBV co-infected female patient enrolled in the “EARNEST trial: a randomized controlled trial to evaluate options for second-line therapy in patients failing a first-line 2NRTI + NNRTI regimen in Africa” who experienced jaundice, chronic diarrhea with dehydration, and oral candidiasis after 60 days of treatment with raltegravir and lopinavir/ritonavir. Abdominal ultrasound on admission revealed bilateral renal parenchymal disease and a normal liver. The patient was treated with intravenous fluids, metronidazole, fluconazole, and metoclopramide. Of note, the patient reported “itching rash all over” one month prior to hospitalization which improved over the course of the month. At the time, the patient was also treated for a urinary tract infection with a 5-day course of amoxicillin. Pertinent laboratory values on admission included ALT 371, AST 246, bilirubin 20, BUN 100, SCr 8.28 (units unknown for all values). Baseline laboratory values are unknown. The patient died one day later with a differential diagnosis including hepatic failure with renal involvement, thrombocytopenia, bacterial sepsis, and potential HBV flare-up. Reviewer’s comments: Causality assessed as possible because the role of raltegravir in the adverse events can’t be excluded. However, the analysis is limited because the case is confounded by use of concomitant medications labeled for hepatic events and the clinical information provided is limited (i.e., unknown baseline liver function, patient’s age, concomitant medications and comorbidities, clinical course, rationale for differential diagnosis list). Amoxicillin is labeled for the risk of hepatic dysfunction under ADVERSE REACTIONS and lopinavir/ritonavir is labeled for the risk of hepatotoxicity, especially in patients with underlying hepatic disease such as HBV, under WARNINGS AND PRECAUTIONS.
8. Case# 9666127 (FDA received date 2013, Mexico, Outcomes: HO, OT) describes a 64-year-old male HCV co-infected patient who developed worsening of hepatic failure and gastrointestinal bleed 184 days after initiation of treatment with raltegravir and emtricitabine/tenofovir. Of note, the patient was also receiving HCV treatment with ribavirin. The patient’s medical history included anemia, ascites, and gastritis. Liver function laboratory values are unknown. At the time of admission, the patient was transfused and received “several unspecified medicines” while antiretroviral therapy and ribavirin were interrupted. At the time of the report the patient had recovered from the events and raltegravir therapy was planned to be resumed. No causality assessment was available. Reviewer’s comments: Causality assessed as possible. The role of raltegravir in the adverse events can’t be excluded but the analysis is limited because the case is confounded by use of concomitant medications labeled for hepatic events and there is missing clinical information (i.e., unknown clinical course, laboratory values, imaging studies, complete list of concomitant medications and comorbidities). Emtricitabine/tenofovir is labeled for the risk of increased liver enzymes, hepatic steatosis, and hepatitis under “Postmarketing Experience”.

8.4 APPENDIX D. DATA MINING RUN OF RALTEGRAVIR AND AN EB05 ≥2.

Generic name	PT or SMQ	N	EB05
Raltegravir	Progressive external ophthalmoplegia	6	86.57
Raltegravir	Immune reconstitution syndrome	75	71.953
Raltegravir	Lipodystrophy acquired	23	59.889
Raltegravir	Virologic failure	11	55.15
Raltegravir	Myelocytosis	5	48.501
Raltegravir	Acute haemorrhagic conjunctivitis	4	47.25
Raltegravir	Vertical talus	4	42.887
Raltegravir	Viral load decreased	4	38.81
Raltegravir	Viral load increased	18	35.658
Raltegravir	Lipodystrophy (SMQ) [narrow]	28	35.625
Raltegravir	Plagiocephaly	9	35.296
Raltegravir	Blood HIV RNA increased	5	29.846
Raltegravir	CD4 lymphocytes decreased	13	27.201
Raltegravir	Mitochondrial toxicity	6	23.869
Raltegravir	Foetal exposure during pregnancy	33	9.842
Raltegravir	Cytolytic hepatitis	28	9.755
Raltegravir	Cachexia	14	7.605
Raltegravir	Small for dates baby	14	7.029
Raltegravir	Hepatitis, non-infectious (SMQ) [narrow]	68	5.985
Raltegravir	Blood creatine phosphokinase increased	45	5.968
Raltegravir	Hepatitis, non-infectious (SMQ) [broad]	68	5.899
Raltegravir	Drug rash with eosinophilia and systemic symptoms	26	5.738
Raltegravir	Eosinophilia	19	5.307
Raltegravir	Oesophageal candidiasis	10	5.257
Raltegravir	Premature baby	27	4.916
Raltegravir	Myopathy	15	4.85
Raltegravir	Maternal exposure during pregnancy	129	4.803
Raltegravir	Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ) [narrow]	172	4.794
Raltegravir	Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ) [broad]	172	4.769
Raltegravir	Neonatal disorders (SMQ) [narrow]	45	4.426
Raltegravir	Graft dysfunction	6	4.402
Raltegravir	Cholestasis	18	4.293
Raltegravir	Cholestasis and jaundice of hepatic origin (SMQ) [narrow]	52	4.209
Raltegravir	Site unspecified biliary disorders (SMQ) [broad]	49	4.154
Raltegravir	Site unspecified biliary disorders (SMQ) [narrow]	49	4.154
Raltegravir	Rash maculo-papular	19	4.144
Raltegravir	Sudden infant death syndrome	5	4.109
Raltegravir	Termination of pregnancy and risk of abortion (SMQ) [broad]	61	4.084

Generic name	PT or SMQ	N	EB05
Raltegravir	Termination of pregnancy and risk of abortion (SMQ) [narrow]	61	4.084
Raltegravir	Neonatal disorders (SMQ) [broad]	47	4.024
Raltegravir	Cholestasis and jaundice of hepatic origin (SMQ) [broad]	52	4.023
Raltegravir	Premature labour	14	3.952
Raltegravir	Hepatotoxicity	17	3.827
Raltegravir	Hepatitis C	14	3.758
Raltegravir	Pregnancy and neonatal topics (SMQ) [narrow]	218	3.623
Raltegravir	Abortion induced	16	3.618
Raltegravir	Rash generalised	28	3.596
Raltegravir	Liver function test abnormal	32	3.591
Raltegravir	Pregnancy and neonatal topics (SMQ) [broad]	220	3.565
Raltegravir	Hepatitis	21	3.48
Raltegravir	Rhabdomyolysis/myopathy (SMQ) [narrow]	38	3.459
Raltegravir	Foetal disorders (SMQ) [narrow]	35	3.454
Raltegravir	Drug related hepatic disorders - severe events only (SMQ) [narrow]	140	3.445
Raltegravir	Drug related hepatic disorders - severe events only (SMQ) [broad]	140	3.434
Raltegravir	Foetal disorders (SMQ) [broad]	35	3.404
Raltegravir	Congenital, familial and genetic disorders (SMQ) [narrow]	71	3.375
Raltegravir	Congenital, familial and genetic disorders (SMQ) [broad]	71	3.375
Raltegravir	Liver infections (SMQ) [narrow]	22	3.374
Raltegravir	Liver infections (SMQ) [broad]	22	3.371
Raltegravir	Aspartate aminotransferase increased	40	3.323
Raltegravir	Alanine aminotransferase increased	42	3.238
Raltegravir	Drug related hepatic disorders - comprehensive search (SMQ) [narrow]	254	3.121
Raltegravir	Stevens-Johnson syndrome	22	3.114
Raltegravir	Hepatic disorders (SMQ) [narrow]	261	3.104
Raltegravir	Drug related hepatic disorders - comprehensive search (SMQ) [broad]	258	3.088
Raltegravir	Drug resistance	10	3.082
Raltegravir	Liver related investigations, signs and symptoms (SMQ) [narrow]	137	3.075
Raltegravir	Hepatic disorders (SMQ) [broad]	266	3.07
Raltegravir	Hepatic failure	22	3.042
Raltegravir	Liver related investigations, signs and symptoms (SMQ) [broad]	141	3.034
Raltegravir	Lipodystrophy (SMQ) [broad]	72	3.03
Raltegravir	Hyperlipidaemia	15	2.984
Raltegravir	Abortion spontaneous	28	2.969
Raltegravir	Mycobacterium avium complex immune restoration disease	3	2.95
Raltegravir	Nephropathy	8	2.945
Raltegravir	Severe cutaneous adverse reactions (SMQ)	45	2.886

Generic name	PT or SMQ	N	EB05
	[narrow]		
Raltegravir	Hepatic encephalopathy	10	2.876
Raltegravir	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) [narrow]	87	2.726
Raltegravir	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) [broad]	87	2.724
Raltegravir	Biliary system related investigations, signs and symptoms (SMQ) [broad]	48	2.698
Raltegravir	Hepatitis cholestatic	8	2.677
Raltegravir	Biliary system related investigations, signs and symptoms (SMQ) [narrow]	36	2.676
Raltegravir	Pneumocystis jiroveci pneumonia	10	2.62
Raltegravir	Jaundice	20	2.616
Raltegravir	Transaminases increased	13	2.572
Raltegravir	Premature rupture of membranes	6	2.479
Raltegravir	Rhabdomyolysis	24	2.476
Raltegravir	Acute pancreatitis (SMQ) [algorithm]	50	2.468
Raltegravir	Renal failure acute	52	2.445
Raltegravir	Dermatitis exfoliative	8	2.394
Raltegravir	Lymphadenopathy	18	2.391
Raltegravir	Foetal death	8	2.373
Raltegravir	Hepatitis fulminant	6	2.35
Raltegravir	Mycobacterium avium complex infection	5	2.34
Raltegravir	Volvulus	5	2.339
Raltegravir	Non-Hodgkin's lymphoma	7	2.299
Raltegravir	Hepatic enzyme increased	24	2.279
Raltegravir	Trisomy 21	5	2.274
Raltegravir	Acute pancreatitis (SMQ) [narrow]	41	2.273
Raltegravir	Neuropathy peripheral	26	2.242
Raltegravir	Pancreatitis acute	14	2.241
Raltegravir	Lactic acidosis (SMQ) [narrow]	13	2.236
Raltegravir	Gastrointestinal mucosal disorder	4	2.235
Raltegravir	Dyslipidaemia (SMQ) [broad]	44	2.18
Raltegravir	Dyslipidaemia (SMQ) [narrow]	44	2.18
Raltegravir	Tubulointerstitial nephritis	9	2.178
Raltegravir	Severe cutaneous adverse reactions (SMQ) [broad]	85	2.165
Raltegravir	Acute renal failure (SMQ) [broad]	140	2.126
Raltegravir	Liver transplant	6	2.117
Raltegravir	Acquired immunodeficiency syndrome	4	2.097
Raltegravir	Hepatitis B	7	2.096
Raltegravir	Acute hepatic failure	9	2.095
Raltegravir	Lymphoma	9	2.068
Raltegravir	Haemolytic anaemia	8	2.065
Raltegravir	Hepatic necrosis	7	2.062
Raltegravir	Ventricular hypertrophy	5	2.051
Raltegravir	Chorioamnionitis	4	2.024
Raltegravir	Acute renal failure (SMQ) [narrow]	106	2.015

Generic name	PT or SMQ	N	EB05
Raltegravir	Myositis	7	2.001

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/s/

DEBRA E BOXWELL
12/18/2014

KELLY Y CAO
12/18/2014

SCOTT E PROESTEL
12/19/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 18, 2014
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 206510
Product Name and Strength: Dutrebis (lamivudine/raltegravir) Tablets, 150 mg/300 mg
Product Type: Multi-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Merck Sharp and Dohme Corp
Submission Date: April 8, 2014
OSE RCM #: 2014-792
DMEPA Primary Reviewer: Mónica Calderón, PharmD, BCPS
DMEPA Associate Director: Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

Merck Sharpe and Dohme Corp is developing Dutrebis for the treatment of HIV-1 under NDA 206510. Thus, the Division of Antiviral Products (DAVP) requested that DMEPA evaluate the Applicant's proposed container label and full prescribing information (FPI) for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C (N/A)
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing a single strength (150 mg/300 mg) combination tablet. The daily dose is 150/300 mg (1 tablet) twice daily and the product will be packaged in 60-count bottles, which is supported by the dosage and administration of this product. DMEPA performed a risk assessment of the proposed container label and FPI and determined the important information is displayed clearly on the label and the Dosage and Administration section is clearly stated within the FPI. The tablet must be swallowed whole and the statement is included in both the Dosage and Administration section and the Patient Counseling Section of the FPI.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes the label and labeling are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dutrebis that Merck Sharp and Dohme Corp submitted on July 11, 2014.

Table 2. Relevant Product Information for Dutrebis	
Active Ingredient	lamivudine/raltegravir
Indication	For use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults, adolescents (16 years of age and older), and pediatric patients (6 through 16 years of age and weighing at least 30 kg)
Route of Administration	Oral
Dosage Form	Tablets
Strength	150 mg/300 mg
Dose and Frequency	Adults and Pediatrics: One tablet twice daily
How Supplied	Unit-of-use bottles of 60 tablets
Storage	Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Dutrebis labels and labeling submitted by Merck Sharp and Dohme Corp on April 8, 2014.

- Container label

G.2 Label and Labeling Images



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

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/s/

MONICA M CALDERON
08/18/2014

IRENE Z CHAN
08/18/2014

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206510

Application Type: New NDA

Name of Drug/Dosage Form: lamivudine/raltegravir

Applicant: Merck Sharp & Dohme Corp.

Receipt Date: April 08, 2014

Goal Date: February 8, 2015

1. Regulatory History and Applicant's Main Proposals

On April 8, 2014, Merck Sharp & Dohme Corp submitted a new 505(b) 2 NDA (206510, lamivudine/raltegravir) a fixed does combination that relies on bioavailability/bioequivalence information containing quality and bridging safety and efficacy material to support the twice daily use of lamivudine and raltegravir 150 mg/300 mg tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 6-16 years of age weighing at least 30 kg. The proposed indication of lamivudine/raltegravir is supported by data along with approved prescribing information for EPIVIR and ISENTRESS.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

In addition, the following labeling issues were identified:

FULL PRESCRIBING INFORMATION: CONTENTS*

1. The same heading for the BOX WARNING that appears in the HIGHLIGHTS and the FULL PRESCRIBING INFORMATION must also appear at the beginning of the table of contents. The heading is slightly different.

FULL PRESCRIBING INFORMATION (FPI): ADVERSE REACTIONS section:

RPM PLR Format Review of the Prescribing Information

2. The following statement should be removed from section (b) (4) and placed at the beginning of sections 6.1, (b) (4): “Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”
3. The following statement should precede the presentation of adverse reactions that have been identified during post approval drug use: (b) (4)

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 11, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

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

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *The length exceeds the page limit however the applicant requested for a waiver for exceeding the one-half page limit.*

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *The horizontal line is not a complete line. The line needs to be fixed and remove the extra line.*

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

Comment:

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

Comment: *Too much white space in Dosage & Administration section*

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Indications & Usage contains unnecessary bullet that needs to be removed*

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

Section	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- NO** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

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

Comment: Spacing issues need to be fixed

Patient Counseling Information Statement in Highlights

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

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

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

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

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

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment: The heading needs to be all in one line (The version I am reviewing complies with this requirement).
- NO** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: The heading is slightly different
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment: Full Prescribing Information should be in lower case

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

- NO** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

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

Comment: .

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

MAMMAH S BORBOR
07/08/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 206510 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: lamivudine/ raltegravir Dosage Form: Tablet Strengths: 150mg/300 mg		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable): N/A		
Date of Application: 04/08/2014 Date of Receipt: 04/08/2014 Date clock started after UN: N/A		
PDUFA Goal Date: February 8, 2015		Action Goal Date (if different): February 6, 2015
Filing Date: June 7, 2014		Date of Filing Meeting: May 23, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) type 4 New combination		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1 infection in adults, and pediatric patients 6-16 years of age weighing at least 30 kg.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
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 or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare 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 (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	

<input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <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 type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input 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)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 113176

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Prprietary name has not been submitted
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Standard
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

authorized signature?					
User Fee Status <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>		Payment for this application: <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			
<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>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm					
If yes, please list below:					
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , 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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<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)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <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) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> 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 FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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

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

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	BE/BA site inspection request is pending
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Mammah look up the date in DARRTS.
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		In the future, you need to look up this information in DARRTS.
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 23, 2014

NDA: 206510

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: lamivudine/raltegravir

DOSAGE FORM/STRENGTH: Tablet 150mg, 300 mg

APPLICANT: Merck Sharp & Dohme Corp.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of HIV-1 infection in adults and pediatric patients 6-16 years of age weighing at least 30 kg.

BACKGROUND: On April 8, 2014, Merck Sharp & Dohme Corp submitted a new 505(b)2 NDA). Merck has not received a right-or-reference for the lamivudine data and they have submitted a Paragraph IV certification. The clinical development program for the combination tablet is based on bridging the safety and efficacy of the combination product to that of the individual components. Bioavailability and bioequivalence and supportive safety data study is the data is essential for approval.

Merck is seeking approval of a twice daily dosing regimen of lamivudine and raltegravir in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 6-16 years of age weighing at least 30 kg.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mammah Borbor	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Islam Younis		Y
Clinical	Reviewer:	Sarita Boyd	Y
	TL:	Kim Struble	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:	Julian O'Rear	Y

Clinical Pharmacology	Reviewer:	Leslie Chinn	Y
	TL:	Islam Younis	Y
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ita Yuen	Y
	TL:	Hanan Ghantous	Y
Biopharmaceutics	Reviewer:	Oko Eradiri	Y
	TL:	Angelica Dorantes	Y
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Mark Seggel	Y
	TL:	Stephen Miller	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Danyal Chaudhry	N
	TL:		
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	N
	TL:		
OPDP	Reviewer:	Jessica Fox Kemi Asante	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Office of Compliance	Rose Xu		Y
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>This 505 (b) (2) NDA relies on the results of a relative bioavailability/bioequivalence (BA/BE) study comparing the fixed-dose combination tablet to the individual components. kg). T</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <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
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</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>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</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>PRODUCT QUALITY (CMC)</p> <p>Comments:</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><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></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><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Mammah Sia Borbor</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <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): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input 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 type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • 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) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<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/

MAMMAH S BORBOR
06/09/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 206510 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: lamivudine/ raltegravir Dosage Form: Tablet Strengths: 150mg/300 mg		
Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable): N/A		
Date of Application: 04/08/2014 Date of Receipt: 04/08/2014 Date clock started after UN: N/A		
PDUFA Goal Date: February 8, 2015		Action Goal Date (if different): February 6, 2015
Filing Date: June 7, 2014		Date of Filing Meeting: May 23, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) type 4 New combination		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1 infection in adults, and pediatric patients 6-16 years of age weighing at least 30 kg.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
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 or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare 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 (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	

Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <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 type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input 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)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 113176

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Prprietary name has not been submitted
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Standard
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

authorized signature?					
User Fee Status <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>		Payment for this application: <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			
<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>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes, please list below:					
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , 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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<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)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <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) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> 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 FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included, 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included, 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<u>Proprietary Name</u>	YES	NO	NA	Comment
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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>REMS</u>	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>Prescription Labeling</u>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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

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

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	BE/BA site inspection request is pending
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Nov. 20, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 23, 2014

NDA: 206510

PROPRIETARY NAME:

ESTABLISHED/PROPER NAME: lamivudine/raltegravir

DOSAGE FORM/STRENGTH: Tablet 150mg, 300 mg

APPLICANT: Merck Sharp & Dohme Corp.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of HIV-1 infection in adults and pediatric patients 6-16 years of age weighing at least 30 kg.

BACKGROUND: On April 8, 2014, Merck Sharp & Dohme Corp submitted a new 505(b)2 NDA for lamivudine and raltegravir fixed-dose combination tablet. Merck has not received a right-of-reference for the lamivudine data and they have submitted a Paragraph IV certification. Isentress (raltegravir) belongs to Merck, however, this application contains a reformulated version of the approved version of raltegravir. The clinical development program for the combination tablet is based on bridging the safety and efficacy of the combination product to that of the individual components. Bioavailability and bioequivalence and supportive safety data are the data considered essential for approval.

Merck is seeking approval of a twice daily dosing regimen of lamivudine and raltegravir that will be used in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 6-16 years of age weighing at least 30 kg.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mammah Borbor	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Islam Younis		Y
Clinical	Reviewer:	Sarita Boyd	Y
	TL:	Kim Struble	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:	Julian O'Rear	Y

Clinical Pharmacology	Reviewer:	Leslie Chinn	Y
	TL:	Islam Younis	Y
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ita Yuen	Y
	TL:	Hanan Ghantous	Y
Biopharmaceutics	Reviewer:	Oko Eradiri	Y
	TL:	Angelica Dorantes	Y
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Mark Seggel	Y
	TL:	Stephen Miller	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Danyal Chaudhry	N
	TL:		
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	N
	TL:		
OPDP	Reviewer:	Jessica Fox Kemi Asante	Y
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Office of Compliance	Rose Xu		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO This 505 (b) (2) NDA relies on the results of a relative bioavailability/bioequivalence (BA/BE) study comparing the fixed-dose combination tablet to the individual components. In addition, the sponsor is relying on the Agency’s previous safety and efficacy findings for lamivudine (the lamivudine labeling). kg). T
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable

<p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <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
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</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>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<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
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<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
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<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
PRODUCT QUALITY (CMC) Comments:	<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
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> Comments:	<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
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></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><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Jeffrey S. Murray, MD, MPH</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <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): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • 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) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<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/

KAREN D WINESTOCK
06/06/2014