CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206510Orig1s000

CHEMISTRY REVIEW(S)

NDA 206510

Dutrebis
(lamivudine and raltegravir) tablets,
150 mg / 300 mg

Merck

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Antiviral Products (DAVP)

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Chemistry Review Data Sheet

1. NDA 206510

2. REVIEW #: 1 Addendum #1

3. REVIEW DATE: 03-FEB-2015

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed (eCTD)	Document Date
Original NDA (0000)	04/08/2014
Labeling / Package Insert (0001)	04/24/2014
Amendment: Master Production Record; Quality Microbiology; Biopharmaceutics (0003)	07/03/2014
Proprietary Name Request (0004)	07/03/14
Labeling / Package Insert (0006)	07/11/14
Amendment: Quality Microbiology (0009)	08/01/2014
Amendment: Biopharmaceutics (0010)	08/29/2014
Labeling / Container / Package Insert (0011)	12/09/2014
Labeling / Package Insert (0012)	12/15/14

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Amendment: Biopharmaceutics; Updated Product Specification (0014)	01/12/2015
Labeling / Container / Package Insert (0015)	01/30/2015
Labeling / Package Insert (0016)	02/03/15

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp and Dohme Corp.
Address:	P.O. Box 2000, 126 East Lincoln Highway RY33-212 Rahway, NJ 07065-0900
Representative(s):	Joanna Pols, Ph.D. Director, Global Regulatory Affairs
Telephone:	732-594-7361
Email:	joanna.pols@merck.com

Reference ID: 3704472

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Dutrebis
   b) Non-Proprietary Name (USAN): lamivudine; raltegravir potassium
   c) Code Name/#: lamivudine:
      raltegravir potassium: MK-0518
   d) CAS Registry Number: lamivudine: CAS-134678-17-4
      raltegravir potassium: CAS-871038-72-1
   e) Chem. Type/Submission Priority:
      i. Chem. Type: # (*fixed dose combination*)
      ii. Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antiretroviral/Systemic/HIV 7030202

11. DOSAGE FORM: Tablets, Immediate Release

12. STRENGTH/POTENCY: 150 mg lamivudine / 300 mg raltegravir

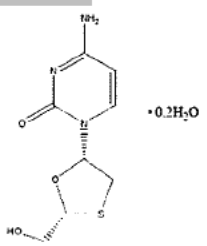
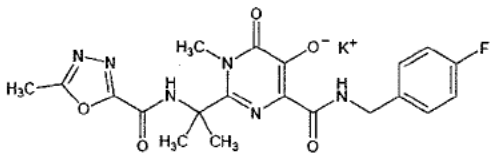
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

    ___X__Not a SPOTS product

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

Lamivudine (b) (4)  Molecular Formula: $C_8H_{11}N_3O_3S \cdot 0.2H_2O$ Molecular weight : 232.86	Raltegravir Potassium:  Molecular Formula: $C_{20}H_{20}FKN_6O_5$ Molecular Mass: 482.51 g/mole

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17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4,7		-	Components identified in NDA; all subject to USP/NF or CFR. See section P.4.
	III			4		-	
	III			4		-	
	III			4		-	
	III			4		-	
	III			4		-	
	III			4		-	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
IND 69928	Raltegravir	
IND 113176	Lamivudine / Raltegravir FDC	See pre-NDA meeting November 20, 2013
NDA 22145	Isentress (raltegravir) Tablets, 400 mg	Approved 10/12/2007; RLD
NDA 203045	Isentress (raltegravir) Chewable Tablets	Approved 12/21/2011
NDA 205786	Isentress (raltegravir) Granules, For Oral Suspension	Approved 12/20/2013
NDA 20564	Epivir (lamivudine) Tablets, 150 mg	Approved 11/17/1995; RLD

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	na		
Mfg. Facilities	Acceptable [*see Attachment A of this review.*]	01/28/15	Rose Xu
Pharm/Tox	na		
ONDQA Biopharmaceutics	Approval	02/02/15	Okpo Eradiri
LNC	na		
DPA Methods Validation	na		
DMEPA	Proprietary name granted	09/12/14	M.Calderon

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EA	Categorical exclusion acceptable	this review	M. Seggel
Quality Microbiology	Approval	08/18/14	Jessica Cole
CDER Office of Testing and Research	na		

19. GOAL DATES

PDUFA Goal:	08-FEB-2015

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The Chemistry Review for NDA 206510

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application, for a fixed dose combination of lamivudine, 150 mg, and raltegravir, 300 mg, in a film-coated tablet, contains chemistry, manufacturing and controls (CMC) data and information in sufficient detail to assure the robust manufacture of drug product with the requisite identity, strength, quality, purity, potency, and bioavailability.

The NDA is recommended for approval from the Product Quality Microbiology and ONDQA Biopharmaceutics perspectives.

Product labeling, including the container label, package insert and patient package insert, have been revised as requested. From the CMC perspective the labeling is complete and factually correct.

Several drug substance and drug product manufacturing, packaging and testing sites are identified in the NDA. Where needed, inspections have been completed. An overall recommendation of Approval has been made for this application [see Attachment A of this review].

This NDA is recommended for approval from the CMC perspective.

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

Not Applicable

II. Summary of Chemistry Assessments

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

Dutrebis is a fixed dose combination of lamivudine (150 mg), a human immunodeficiency virus (HIV-1) nucleoside reverse transcriptase inhibitor (NRTI) and raltegravir (300 mg), a HIV-1 integrase strand transfer inhibitor (INSTI). Both lamivudine, a BCS Class 1 drug, and raltegravir, a BCS Class II drug, are currently available in single-component drug products. Glaxo's NDA 20564, for Epivir (lamivudine) film coated tablets, 150 mg, was approved in 1995 (a 300 mg tablet was subsequently approved). Merck's NDA 22145, for Isentress (raltegravir) Tablets, 400 mg, was approved in 2007. Both products are dosed twice daily. In order to provide a

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convenient, simple, and cost effective treatment option for patients receiving chronic antiviral therapy, Merck developed a fixed dose combination of lamivudine and raltegravir in a tablet for twice daily administration with no food restrictions. Formulation development targeted a product with in vivo exposure (b) (4) (b) (4), and with quality attributes consistent with the expected safety and efficacy.

The 400 mg Isentress Tablet formulation, with its 869 mg tablet weight, did not lend itself for developing an (b) (4) fixed dose combination product (b) (4) (b) (4) (b) (4) Ultimately, a FDC tablet containing 150 lamivudine and 300 mg raltegravir, and weighing only 776 mg, was developed for commercialization. Inactive ingredients include hydroxypropyl methylcellulose, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The 15.88 mm x 8.61 mm oval (b) (4) tablet has an (b) (4) film coating to (b) (4) The non-functional film coating contains hypromellose, lactose monohydrate, triacetin, yellow iron oxide, FD&C Blue #2, and titanium dioxide.

Lamivudine (b) (4) and raltegravir (b) (4) are manufactured (b) (4) (b) (4)

While the applicant did not apply a formal Quality by Design approach to formulation and process development, the principles of ICH Q8-Q11 were applied. Merck conducted risk assessments focused on the components of the formulation and on each manufacturing process train. Based on the product and process knowledge gained, potential risks to product quality have been minimized.

The overall control strategy includes raw material controls, manufacturing within proven acceptable ranges (PARs), in-process controls, packaging in a suitable container closure system, a regulatory product specification, and ongoing stability testing. The regulatory specification includes tests for appearance, identity of the actives, assay of each active, degradation products, moisture content, and dissolution. The specification ensures that the drug product has the requisite identity, strength, quality, purity, potency and bioavailability.

The drug product is packaged in 60-count HDPE bottles with (b) (4) closures. A (b) (4) desiccant is included in each bottle (b) (4). Based on ongoing stability studies the drug product can be stored in the original container, with

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desiccant, at room temperature for 24 months. Long-term stability studies are being conducted at 25°C/60% RH. Studies at 30°C/75% RH, which would support use in Climatic Zone 4, have not been reported.

Lamivudine drug substance used in the manufacture of Dutrebis is manufactured and tested according to the CMC documentation submitted in the current NDA. It is manufactured for Merck (b) (4)

(b) (4)

Lamivudine drug substance is the subject of USP and Ph.Eur. monographs. (b) (4)

(b) (4)

Raltegravir is manufactured as the potassium salt according to the process documented in Merck's approved Isentress NDA (22145). Chemistry, manufacturing and controls information is by cross-reference to NDA 22145. Raltegravir potassium is also manufactured for Merck at (b) (4). Because raltegravir is introduced into the product as the potassium salt, product labeling must comply with the salt nomenclature policy and strength expressed (b) (4) (i.e., 300 mg) with a statement of equivalency to 325.8 mg potassium salt.

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

Dutrebis is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. The maximum dose of Dutrebis is one tablet (150 mg lamivudine/300 mg raltegravir), twice daily, with or without food.

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Dutrebis Tablets, 60-count HDPE bottles are labeled for storage at 20-25°C (excursions permitted between 15-30°C), see USP Controlled Room Temperature. An initial expiration dating period of 24-months has been established.

C. Basis for Approvability or Not-Approval Recommendation

Lamivudine drug substance CMC provided in the current NDA is adequate to ensure the identity, strength, quality and purity of lamivudine used in the manufacture of Dutrebis Tablets.

Raltegravir drug substance CMC is adequately documented in NDA 22145. The [redacted] (b) (4) process is adequately documented in the current application. Sufficient controls have been established to ensure the identity, strength, quality and purity of raltegravir used in the manufacture of Dutrebis Tablets.

Product and process knowledge gained during development and scale-up has resulted in a robust manufacturing process that will consistently yield drug product with the identity, strength, quality, purity, potency, and bioavailability required for safe and effective use by HIV patients.

The applicant has adequately validated the analytical procedures. Merck recently submitted (ectd seq. no. 0014, 01/12/15) an update to the drug product assay / degradation product method to enhance robustness. The reported changes to the sample preparation procedure are supported by additional validation data. Because the product does not contain new molecular entities and the procedures are relatively straightforward (i.e., RP-HPLC, compendial tests), verification of the tests by FDA's St. Louis laboratory was not requested.

Dr. Jessica Cole, OPS/NDMS, has concluded that there is acceptable control of product quality microbiology. Dr. Okpo Eradiri, ONDQA Biopharmaceutics, reviewed the bioequivalence study and dissolution test report. The applicant has agreed to tighten the dissolution test acceptance criterion [redacted] (b) (4) to Q=[redacted] (b) (4) % at 30 minutes. The application is now recommended for approval from the Biopharmaceutics perspective.

Based on recent inspections and profile class history, the drug substance and drug product manufacturing, packaging and testing sites have acceptable CGMP status. An overall recommendation of approval of the application has been issued by OPQ/OPF (formerly OMPQ, Office of Compliance). See Attachment A of this review for a copy of the Panorama inspection view.

Initial comments regarding labeling (bottle label, package insert and patient package insert) have been conveyed to the applicant by the review team. From the CMC perspective, the primary revision necessary was addition of statement of the equivalency of 328.8 mg raltegravir potassium to 300 mg of the [redacted] (b) (4) in accordance with the salt nomenclature policy. Overall, the labeling is complete and

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accurate from the CMC perspective. Further revisions to improve readability have been made to the labeling as requested by FDA (ectd seq. no. 0015, 01/30/15). The revised labeling as submitted on 30-JAN-2015 is acceptable from the CMC perspective. Minor "non-cmc" changes to the package insert were requested by the review team. A revised package insert was submitted was submitted on February 3, 2015 (ectd seq. no. 0016). The labeling remains acceptable from the CMC perspective.

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III. Lifecycle Knowledge Management

RISK IDENTIFICATION [*note: completed concurrently with review*]

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any (+) = considerations that increase risk (-) = considerations that reduce risk
Assay (Lamivudine, Raltegravir)	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	2	3	2	12	
Related substances / Degradants	"	2	2	3	12	(b) (4)
Lamivudine CU	"	2	2	2	8	
Raltegravir CU	"	2	2	2	8	
(b) (4)	"	2	3	2	12	
Lamivudine (b) (4) (b) (4)	"	2	2	4	16	
Raltegravir (b) (4) (b) (4)	"	2	2	4	16	
Appearance / Elegance	"	2	3	1	6	
Dissolution [a]	"					
Microbiological [b]	"				Low	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

a See ONDQA Biopharmaceutics Review; b See Product Quality Microbiology Review

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RISK MITIGATION AND LIFECYCLE CONSIDERATIONS

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach / Control Strategy	Risk Evaluation [Acceptable/ Not Acceptable]	Lifecycle Considerations/ Comments**
Lamivudine Assay	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	12		Acceptable	
Raltegravir Assay	"	12	(b) (4)	Acceptable	
Related substances / Degradants	"	12		Acceptable	
Lamivudine Content Uniformity	"	8		Acceptable	
Raltegravir Content Uniformity	"	8		Acceptable	
(b) (4)	"	12		Acceptable	
Raltegravir API (b) (4) (b) (4)	"	16		Acceptable	
Lamivudine (b) (4) (b) (4)	"	16		Acceptable	
Appearance / Elegance	"	6		Acceptable	
Dissolution [a]	"				
Microbiological [b]	"	*Low*		Acceptable	

* Risk ranking applies to product attribute/CQA ([redacted], M, and [redacted])

** For example, post marketing commitment, knowledge management post approval, etc. {e.g. Continue monitoring, especially during stability studies}

a See ONDQA Biopharmaceutics Review.

b See Product Quality Microbiology Review: "Reviewer Comments – The microbiological quality of the drug product is controlled via an adequate upstream control strategy and a suitable stability testing protocol."

IV. Administrative

A. Reviewer's Signature

{ electronic signature}
Mark R. Seggel, Chemistry Reviewer

Mark R. Seggel -S
Digitally signed by Mark R. Seggel -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -S, 0.9.2342.19200300.100.1.1=13000715 39
Date: 2015.02.05 09:06:49 -05'00'

B. Endorsement Block

{ electronic signature}
Dorota Matecka, Ph.D., Acting Branch Chief

Dorota M. Matecka -S
Digitally signed by Dorota M. Matecka -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001 23291, cn=Dorota M. Matecka -S
Date: 2015.02.05 11:59:12 -05'00'

C. CC Block

NDA 206510 Review Team

20 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3704472

NDA 206510

Dutrebis
(lamivudine and raltegravir) tablets,
150 mg / 300 mg

Merck

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Antiviral Products (DAVP)

Reference ID: 3704472

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Chemistry Review Data Sheet

1. NDA 206510

2. REVIEW #: 1

3. REVIEW DATE: 31-DEC-2014

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Not Applicable	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)	Document Date
Original NDA (0000)	04/08/2014
Labeling / Package Insert (0001)	04/24/2014
Amendment: Master Production Record; Quality Microbiology; Biopharmaceutics (0003)	07/03/2014
Proprietary Name Request (0004)	07/03/14
Labeling / Package Insert (0006)	07/11/14
Amendment: Quality Microbiology (0009)	08/01/2014
Amendment: Biopharmaceutics (0010)	08/29/2014
Labeling / Container / Package Insert (0011)	12/09/2014
Labeling / Package Insert (0012)	12/15/14

7. NAME & ADDRESS OF APPLICANT:

Name:	Merck Sharp and Dohme Corp.
Address:	P.O. Box 2000, 126 East Lincoln Highway RY33-212 Rahway, NJ 07065-0900
Representative(s):	Joanna Pols, Ph.D. Director, Global Regulatory Affairs
Telephone:	732-594-7361
Email:	joanna.pols@merck.com

Reference ID: 3704472

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Dutrebis
   b) Non-Proprietary Name (USAN): lamivudine; raltegravir potassium
   c) Code Name/#: lamivudine:
      raltegravir potassium: MK-0518
   d) CAS Registry Number: lamivudine: CAS-134678-17-4
      raltegravir potassium: CAS-871038-72-1
   e) Chem. Type/Submission Priority:
      i. Chem. Type: # (*fixed dose combination*)
      ii. Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antiretroviral/Systemic/HIV 7030202

11. DOSAGE FORM: Tablets, Immediate Release

12. STRENGTH/POTENCY: 150 mg lamivudine / 300 mg raltegravir

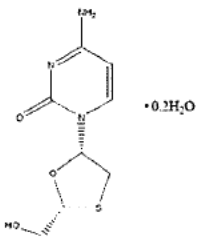
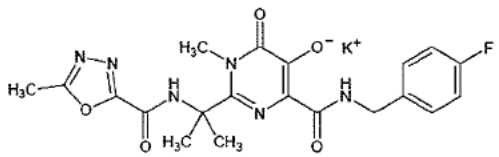
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

    ___X__Not a SPOTS product

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

Lamivudine (b) (4)	Raltegravir Potassium:
 Molecular Formula: $C_8H_{11}N_3O_3S \cdot 0.2H_2O$ Molecular weight : 232.86	 Molecular Formula: $C_{20}H_{20}FKN_6O_5$ Molecular Mass: 482.51 g/mole

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17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	4,7		-	Components identified in NDA; all subject to USP/NF or CFR. See section P.4.
	III			4		-	
	III			4		-	
	III			4		-	
	III			4		-	
	III			4		-	
	III			4		-	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
IND 69928	Raltegravir	
IND 113176	Lamivudine / Raltegravir FDC	See pre-NDA meeting November 20, 2013
NDA 22145	Isentress (raltegravir) Tablets, 400 mg	Approved 10/12/2007; RLD
NDA 203045	Isentress (raltegravir) Chewable Tablets	Approved 12/21/2011
NDA 205786	Isentress (raltegravir) Granules, For Oral Suspension	Approved 12/20/2013
NDA 20564	Epivir (lamivudine) Tablets, 150 mg	Approved 11/17/1995; RLD

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	na		
EES / OMPQ	*pending*		
Pharm/Tox			
ONDQA Biopharmaceutics	*pending*		Okpo Eradiri
LNC	na		
DPA Methods Validation	na		
DMEPA	Proprietary name granted		
EA	Categorical exclusion acceptable	this review	M. Seggel

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Quality Microbiology	Approval	08/18/14	Jessica Cole
CDER Office of Testing and Research	na		

19. GOAL DATES

GRMP Goal:	04-JAN-2045
PDUFA Goal:	08-FEB-2015

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The Chemistry Review for NDA 206510

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application, for a fixed dose combination of lamivudine, 150 mg, and raltegravir, 300 mg, in a film-coated tablet, contains chemistry, manufacturing and controls (CMC) data and information in sufficient detail to assure the robust manufacture of drug product with the requisite identity, strength, quality, purity, potency, and bioavailability.

The NDA is recommended for approval from the Product Quality Microbiology perspective. A final recommendation from ONDQA Biopharmaceutics is pending, but is expected to be favorable.

Product labeling, including the container label, package insert and patient package insert, have been revised as requested. From the CMC perspective the labeling is complete and factually correct, although some editorial revisions may be warranted.

Several drug substance and drug product manufacturing, packaging and testing sites are identified in the NDA. Where needed, inspections have been completed. However, the Office of Compliance has not yet issued an overall recommendation for this application.

Upon receipt of a recommendation for approval from ONDQA Biopharmaceutics, agreement on all aspects of the labeling, and issuance of an overall acceptable recommendation from the Office of Compliance, this NDA will be recommended for approval from the CMC perspective.

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

Not Applicable

II. Summary of Chemistry Assessments

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

Dutrebis is a fixed dose combination of lamivudine (150 mg), a human immunodeficiency virus (HIV-1) nucleoside reverse transcriptase inhibitor (NRTI) and raltegravir (300 mg), a HIV-1 integrase strand transfer inhibitor (INSTI). Both

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lamivudine, a BCS Class 1 drug, and raltegravir, a BCS Class II drug, are currently available in single-component drug products. Glaxo's NDA 20564, for Epivir (lamivudine) film coated tablets, 150 mg, was approved in 1995 (a 300 mg tablet was subsequently approved). Merck's NDA 22145, for Isentress (raltegravir) Tablets, 400 mg, was approved in 2007. Both products are dosed twice daily. In order to provide a convenient, simple, and cost effective treatment option for patients receiving chronic antiviral therapy, Merck developed a fixed dose combination of lamivudine and raltegravir in a tablet for twice daily administration with no food restrictions. Formulation development targeted a product with in vivo exposure (b) (4) (b) (4), and with quality attributes consistent with the expected safety and efficacy.

The 400 mg Isentress Tablet formulation, with its 869 mg tablet weight, did not lend itself for developing an (b) (4) fixed dose combination product. (b) (4) (b) (4) (b) (4) Ultimately, a FDC tablet containing 150 lamivudine and 300 mg raltegravir, and weighing only 776 mg, was developed for commercialization. Inactive ingredients include hydroxypropyl methylcellulose, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The 15.88 mm x 8.61 mm oval (b) (4) tablet has an (b) (4) film coating to (b) (4) The non-functional film coating contains hypromellose, lactose monohydrate, triacetin, yellow iron oxide, FD&C Blue #2, and titanium dioxide.

Lamivudine (b) (4) and raltegravir (b) (4) are manufactured using (b) (4) (b) (4)

While the applicant did not apply a formal Quality by Design approach to formulation and process development, the principles of ICH Q8-Q11 were applied. Merck conducted risk assessments focused on the components of the formulation and on each manufacturing process train. Based on the product and process knowledge gained, potential risks to product quality have been minimized.

The overall control strategy includes raw material controls, manufacturing within proven acceptable ranges (PARs), in-process controls, packaging in a suitable container closure system, a regulatory product specification, and ongoing stability testing. The regulatory specification includes tests for appearance, identity of the actives, assay of each active, degradation products, moisture content, and dissolution. The specification

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ensures that the drug product has the requisite identity, strength, quality, purity, potency and bioavailability.

The drug product is packaged in 60-count HDPE bottles with (b) (4) closures. A (b) (4) desiccant is included in each bottle (b) (4). Based on ongoing stability studies the drug product can be stored in the original container, with desiccant, at room temperature for 24 months. Long-term stability studies are being conducted at 25°C/60% RH. Studies at 30°C/75% RH, which would support use in Climatic Zone 4, have not been reported.

Lamivudine drug substance used in the manufacture of Dutrebis is manufactured and tested according to the CMC documentation submitted in the current NDA. It is manufactured for Merck at (b) (4)

(b) (4)

Lamivudine drug substance is the subject of USP and Ph.Eur. monographs. (b) (4)

(b) (4)

Raltegravir is manufactured as the potassium salt according to the process documented in Merck's approved Isentress NDA (22145). Chemistry, manufacturing and controls information is by cross-reference to NDA 22145. Raltegravir potassium is also manufactured for Merck at (b) (4) Because raltegravir is introduced into the product as the potassium salt, product labeling must comply with the salt nomenclature policy and strength expressed as (b) (4) (i.e., 300 mg) with a statement of equivalency to 325.8 mg potassium salt.

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

Dutrebis is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents. The maximum dose of Dutrebis is one tablet (150 mg lamivudine/300 mg raltegravir), twice daily. Dutrebis tablets must be swallowed whole.

Dutrebis Tablets, 60-count HDPE bottles are labeled for storage at 20-25°C (excursions permitted between 15-30°C), see USP Controlled Room Temperature. An initial expiration dating period of 24-months has been established.

C. Basis for Approvability or Not-Approval Recommendation

Lamivudine drug substance CMC provided in the current NDA is adequate to ensure the identity, strength, quality and purity of lamivudine used in the manufacture of Dutrebis Tablets.

Raltegravir drug substance CMC is adequately documented in NDA 22145. The (b) (4) process is adequately documented in the current application. Sufficient controls have been established to ensure the identity, strength, quality and purity of raltegravir used in the manufacture of Dutrebis Tablets.

Product and process knowledge gained during development and scale-up has resulted in a robust manufacturing process that will consistently yield drug product with the identity, strength, quality, purity, potency, and bioavailability required for safe and effective use by HIV patients.

The applicant has adequately validated the analytical procedures. Because the procedures are relatively straightforward, verification of the tests by FDA's St. Louis laboratory was not requested.

Dr. Jessica Cole, OPS/NDMS, has concluded that there is acceptable control of product quality microbiology.

Dr. Okpo Eradiri, ONDQA Biopharmaceutics, has reviewed the bioequivalence study and dissolution test report. A final recommendation is pending, but is expected to be for approval.

An overall recommendation by the Office of Compliance is pending. It is expected that, based on recent inspections and profile class history, the drug substance and drug product manufacturing, packaging and testing sites will have acceptable CGMP status, and approval of the application will be recommended.

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Initial comments regarding labeling (bottle label, package insert and patient package insert) have been conveyed to the applicant by the review team. From the CMC perspective, the primary revision necessary was addition of statement of the equivalency of 328.8 mg raltegravir potassium to 300 mg of the (b) (4) in accordance with the salt nomenclature policy. Overall, the labeling is complete and accurate from the CMC perspective, although editorial revisions related to the salt equivalency statement should be considered.

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III. Lifecycle Knowledge Management

RISK IDENTIFICATION [*note: completed concurrently with review*]

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any (+) = considerations that increase risk (-) = considerations that reduce risk
Assay (Lamivudine, Raltegravir)	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	2	3	2	12	
Related substances / Degradants	"	2	2	3	12	(b) (4)
Lamivudine CU	"	2	2	2	8	
Raltegravir CU	"	2	2	2	8	
(b) (4)	"	2	3	2	12	
Lamivudine (b) (4) (b) (4)	"	2	2	4	16	
Raltegravir (b) (4) (b) (4)	"	2	2	4	16	
Appearance / Elegance	"	2	3	1	6	
Dissolution [a]	"					
Microbiological [b]	"				*Low*	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

a See ONDQA Biopharmaceutics Review; b See Product Quality Microbiology Review

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RISK MITIGATION AND LIFECYCLE CONSIDERATIONS

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach / Control Strategy	Risk Evaluation [Acceptable/ Not Acceptable]	Lifecycle Considerations/ Comments**
Lamivudine Assay	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	12		Acceptable	
Raltegravir Assay	"	12	(b) (4)	Acceptable	
Related substances / Degradants	"	12		Acceptable	
Lamivudine Content Uniformity	"	8		Acceptable	
Raltegravir Content Uniformity	"	8		Acceptable	
(b) (4)	"	12		Acceptable	
Raltegravir API (b) (4) (b) (4)	"	16		Acceptable	
Lamivudine API (b) (4) (b) (4)	"	16		Acceptable	
Appearance / Elegance	"	6		Acceptable	
Dissolution [a]	"				
Microbiological [b]	"	*Low*		Acceptable	

* Risk ranking applies to product attribute/CQA (L, M, and H)

** For example, post marketing commitment, knowledge management post approval, etc. {e.g. Continue monitoring, especially during stability studies}

a See ONDQA Biopharmaceutics Review.

b See Product Quality Microbiology Review: "Reviewer Comments – The microbiological quality of the drug product is controlled via an adequate upstream control strategy and a suitable stability testing protocol."

IV. Administrative

A. Reviewer's Signature

{ electronic signature}
Mark R. Seggel, Chemistry Reviewer

Mark R. Seggel -A
Digitally signed by Mark R. Seggel -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -A, 0.9.2342.19200300.100.1.1=1300071539
Date: 2014.12.31 13:27:49 -05'00'

B. Endorsement Block

{ electronic signature}
Dorota Matecka, Ph.D., DAIP CMC Lead and Secondary Reviewer

Dorota M. Matecka -S
Digitally signed by Dorota M. Matecka -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300123291, cn=Dorota M. Matecka -S
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C. CC Block

NDA 206510 Review Team

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