

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204790Orig1s000**

**CHEMISTRY REVIEW(S)**

ONDQA Division Director's Memo  
NDA 204790, TIVICAY (dolutegravir) Tablets, 50 mg  
Date: 25-JUL-2013

## Introduction

TIVICAY (dolutegravir) Tablets, 50 mg, are formulated as immediate release, yellow, film-coated tablets for oral administration.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance was issued on 23-JUL-2013.

*All CMC review issues have been resolved, and ONDQA recommends approval of this NDA.*

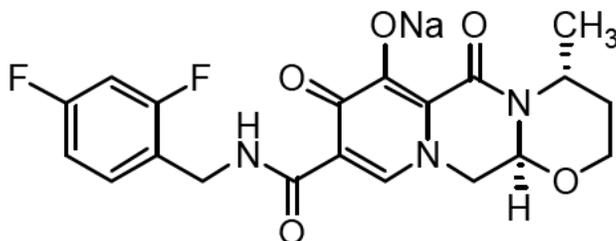
## Administrative

The original submission of this 505(b)(1) NDA was received on 17-DEC-2012. Several solicited CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (17-MAY-2013 by Dr. Lin Qi and Dr. Maotang Zhou), Chemistry Review #1 - Addendum (24-JUL-2013 by Dr. Lin Qi and Dr. Maotang Zhou) and the Biopharmaceutics Review (15-MAY-2013, Dr. D. Lakhani).

The NDA is supported by IND (b)(4) and one (1) drug master file (DMF). The cross-referenced DMF was assessed for adequacy in the respective chemistry review.

## Drug Substance (dolutegravir)

Chemical Name: Sodium (4*R*,12*aS*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12*a*-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate



Molecular Formula C<sub>20</sub>H<sub>18</sub>F<sub>2</sub>N<sub>3</sub>O<sub>5</sub>Na  
Molecular Weight 441.4 g/mol (dolutegravir sodium)

Dolutegravir is a new molecular entity. It possesses two chiral centers and is manufactured as its sodium salt. (b)(4)

(b)(4)  
Dolutegravir is slightly soluble in water and practically insoluble in 2-propanol and ethanol.

Dolutegravir is relatively stable; no extraordinary storage precautions are required. The proposed re-test period (b) (4) when stored in the recommended container closure system and under the proposed storage conditions (up to 30°C, protected from light) is granted.

### **Drug Product – TIVICAY Tablets, 50 mg**

TIVICAY Tablets are formulated as an immediate release tablet intended for oral administration. Each tablet contains 52.6 mg of dolutegravir sodium which is equivalent to 50 mg of dolutegravir free acid. The formulation contains (b) (4) dolutegravir sodium, and the inactive ingredients D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide. All excipients comply with USP and are commonly used in conventional solid oral formulations.

The manufacturing process consists of (b) (4)  
During the review clock, the team noted one deficiency (b) (4)  
As a result, the Applicant agreed to a post-marketing commitment to address the issue. As captured in the Chemistry Review, these deficiencies were resolved during the review clock. Acceptable container/carton labeling was received on 12-JUN-2013.

Based on the stability data provided and in accordance with ICH Q1E, the Agency grants a 24 month expiry for this product. The following language should be inserted into the action letter when issued:

*“Based on the provided stability data, the Agency grants a shelf life of 24 months for Dolutegravir Tablets, 50 mg, when stored in the primary packaging [30 (b) (4) fill count] at 25°C (77°F); excursions permitted from 15 to 30°C (59° – 86°F).”*

Additionally, the following CMC postmarketing commitment should be stated in the action letter:

*“Conduct the requested (b) (4) testing for drug substance to target (b) (4) degradation, evaluate both drug substance and drug product impurities methods using these conditions, and submit the data as a Changes Being Effected in 0 Days Supplement to be filed within 6 months from the date of NDA action.”*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SARAH P MIKSINSKI  
07/25/2013

# **NDA 204790**

**TIVICAY® (Dolutegravir) Tablets, 50 mg**

**ViiV Healthcare Company  
(US Agent: GSK)**

**Lin Qi, Ph.D.  
and  
Maotang Zhou, Ph.D.**

**Review Chemists**

**Office of New Drug Quality Assessment  
Division II, Branch V**

**For the Division of Anti-Viral Products**

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# CMC Review Data Sheet

1. NDA 204790
2. REVIEW #: 1 - Addendum
3. REVIEW DATE: 24-July-2013
4. REVIEWERS: Lin Qi (Drug Product) and Maotang Zhou (Drug Substance)
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 75,382 submission	07-AUG-2007
Original IND 75,382 CMC review by A. Yu	10-JAN-2008
CMC end-of-phase-2 meeting	18-AUG-2010
CMC only pre-NDA meeting	25-JUL-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA Submission	17-DEC-2012
Amendment (Response to Quality Information request (IR))	15-MAR-2013
Amendment (Response to Quality IR)	29-MAR-2013
Amendment (Response to Quality IR)	08-APR-2013
Amendment (Response to Quality IR)	14-May-2013
Amendment (Labeling)	12-Jun-2013
Amendment (Labeling)	9-Jul-2013

7. NAME & ADDRESS OF APPLICANT:

Name: ViiV Healthcare Company  
Address: GlaxoSmithKline, PO BO 13398, Bldg5  
5218 Five Moore Drive  
Reach Triangle Park, NC 27709

Representative: Martha Anne Auld, R.Ph.  
Telephone: 919-315-8319

## CMC Review Data Sheet

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

- a) Proprietary Name: Tivicay®  
b) Non-Proprietary Name: Dolutegravir Sodium  
c) Code Name/# (ONDQA only):  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type:
  - Submission Priority: P

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

## 10. PHARMACOL. CATEGORY: Antiviral

## 11. DOSAGE FORM: Tablets (film-coated)

## 12. STRENGTH/POTENCY: 50 mg

## 13. ROUTE OF ADMINISTRATION: Oral

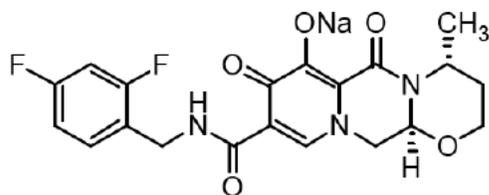
14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

Sodium (4*R*,12*aS*)-9-{-[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12*a*-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate



$C_{20}H_{18}F_2N_3NaO_5$

441.36 g/mol (dolutegravir sodium)

419.38 g/mol (dolutegravir free acid)

CMC Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4			LOA Date: 2/24/2012

<sup>1</sup> 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")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	(b) (4)

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	23-July-2013	EES-PROD
Pharm/Tox	N/A		
Biopharm	Acceptable	16-MAY-2013	Deepika Arora Lakhani
LNC	N/A		
Methods Validation	Acceptable	14-MAY-2013	Michael L Trehy
DMEPA*			
EA	Categorical exclusion (see review)	19-APR-2013	Lin Qi and Maotang Zhou
Microbiology	Acceptable	22-MAY-2013	Stephen Langille

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 204-790

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of **TIVICAY** (dolutegravir) Tablets, 50 mg. The labeling and package insert as amended contain adequate CMC information. The Office of Compliance has provided an overall recommendation of "Acceptable" for the establishments filed in this NDA, as of July 23, 2013. From the CMC perspective, this NDA is recommended for approval.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments

Conduct the requested [REDACTED] (b) (4) testing for drug substance to target [REDACTED] (b) (4) degradation, evaluate both drug substance and drug product impurities methods using these conditions, and submit the data as a Changes Being Effected in 0 Days Supplement to be filed within 6 months from the date of NDA action.

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

The drug substance, dolutegravir sodium (GSK1349572A), is a white to light yellow powder, with a molecular formula of  $C_{20}H_{18}F_2N_3NaO_5$ . Dolutegravir is a new molecular entity (NME). Dolutegravir sodium is manufactured, controlled, packaged, and stability-tested at [REDACTED] (b) (4) [REDACTED] Shionogi Pharma Chemicals Co., Ltd., Japan. The drug substance is manufactured [REDACTED] (b) (4) [REDACTED]. The description on manufacturing processes and controls for dolutegravir sodium, as amended, is adequate. The specification for the drug substance contains appropriate acceptance criteria for description, identification, sodium content, assay, related substances, residual solvents, water content, solid state form, particle size distribution, and heavy metals. Available batch analysis and stability data are within specifications. The six potential genotoxic impurities identified are adequately controlled by the manufacturing process to levels of no more than (NMT) [REDACTED] (b) (4) [REDACTED] in the final drug substance, and are not included in the drug substance specification. The solid state form of the drug substance is verified by an identity test [REDACTED] (b) (4) [REDACTED] (u) (4) [REDACTED]. Data was provided to demonstrate [REDACTED] (b) (4) [REDACTED] (u) (4) does not impact drug product dissolution. The drug substance is stored [REDACTED] (u) (4) [REDACTED].

## Executive Summary Section

(b) (4) Eighteen (18)-month long term (30 °C/65%RH and 25 °C/60% RH) and 6-month accelerated (40 °C/75% RH) stability data for three commercial scale primary stability batches of dolutegravir sodium drug substance are provided. The data supports the proposed retest period (b) (4) for the drug substance when stored up to 30 °C (86°F) and protected from light.

## (2) Drug Product

**TIVICAY** (dolutegravir) Tablets, 50 mg, is an immediate release, yellow film coated, round, biconvex tablet for oral administration. Tablets are debossed with 'SV 572' on one side and '50' on the other side. Each tablet contains 52.6 mg dolutegravir sodium, which is equivalent to 50 mg dolutegravir free acid. The formulation contains (b) (4) dolutegravir sodium, and the inactive ingredients D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide. All excipients comply with USP and are within levels used in other approved drug products.

Dolutegravir Tablets, 50 mg, are manufactured (b) (4)

(b) (4) A risk management approach was applied during process development. A few ranges/targets of variables were investigated using pilot and production scale DoE or during production scale manufacture of clinical batches (b) (4)

(b) (4) identified as critical process parameters (CPP). Fixed ranges/targets were preselected for most variables and excluded from investigation. Although these are identified as non-critical process parameters (NCPP), changes to some NCPPs could impact product quality. The applicant has agreed to assess impact on quality when NCPPs are changed. The proposed control strategy (See P.2.3.3) includes controls on drug substance attributes (See P.2.1.1), unit operation controls (See P.2.3.1), and drug product controls (See P.5.6). The drug product will be tested for Description, Identification, Content, Uniformity of Content, Drug-Related Impurities, and Dissolution, and Microbiological quality at release. The acceptance criteria are justified appropriately.

Although the HPLC test methods for drug substance and drug product were determined to be overall adequate for NDA approval by both CMC reviewers of this NDA and FDA St. Louis lab, the applicant had used a (b) (4) test condition during method development. Therefore, a post-marketing commitment was set up as described in Section I.B. to further evaluate the methods.

The biopharmaceutics review dated May 16, 2013 concluded the dissolution test method was discriminating. The drug substance particle size, (b) (4) design space and (b) (4) design space were supported by dissolution data. Although there was insufficient dissolution data to support the extremes of the design space, the review concluded that the dissolution acceptance criteria ( $Q = (b) (4)$  at 20 min) is likely to reject batches with dissimilar dissolution profiles.

## Executive Summary Section

There are no drug product changes in assay, appearance, impurities, or solid state form upon storage in the primary container during long-term (25°C/60% RH and 30°C/75% RH), accelerated (40°C/75% RH), 50°C/ambient, freeze/thaw cycle (-20°C/30°C), exposed photostability stability studies. (b) (4)

The available stability data support a shelf life of 24 months for Dolutegravir Tablets, 50 mg, when stored in the primary packaging at 25°C (77°F); excursions permitted 15 to 30°C (59 to 86°F).

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

TIVICAY® is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults and children aged 12 years and older. TIVICAY Tablets may be taken with or without food. The recommended dose of TIVICAY is 50 mg administered orally once daily or twice daily.

**C. Basis for Approvability or Not-Approval Recommendation**

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, test methods, specifications, batch data and stability data for assuring consistent product quality of the drug substance and drug product over the storage period. The CMC information in the NDA, as amended, is sufficient to assure the identity, strength, purity, and quality of TIVICAY (dolutegravir) Tablets, 50 mg over the shelf-life granted.

The labeling and package insert as amended contain adequate CMC information.

The product quality microbiological review dated May 22, 2013 recommended for approval.

The Office of Compliance has provided an overall recommendation of “Acceptable” for the establishments filed in this NDA, as of July 23, 2013.

Therefore, from the CMC perspective, this NDA is recommended for approval.

## Executive Summary Section

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

*(See appended electronic signature page)*

Lin Qi, Ph.D. and Maotang Zhou, Ph.D., CMC Reviewers, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Rapti Madurawe, Ph.D., Branch Chief, Branch V, ONDQA

**C. CC Block:** entered electronically in DARRTS

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/s/  
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LIN QI  
07/24/2013

MAOTANG ZHOU  
07/24/2013

RAPTI D MADURawe  
07/24/2013

# **NDA 204790**

**TIVICAY® (Dolutegravir) Tablets, 50 mg**

**ViiV Healthcare Company  
(US Agent: GSK)**

**Lin Qi, Ph.D.  
And  
Maotang Zhou, Ph.D.**

**Review Chemists**

**Office of New Drug Quality Assessment  
Division II, Branch V**

**For the Division of Anti-Viral Products**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 204790
2. REVIEW #: 1
3. REVIEW DATE: 17-MAY-2013
4. REVIEWERS: Lin Qi (Drug Product) and Maotang Zhou (Drug Substance)
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 75,382 submission	07-AUG-2007
Original IND 75,382 CMC review by A. Yu	10-JAN-2008
CMC end-of-phase-2 meeting	18-AUG-2010
CMC only pre-NDA meeting	25-JUL-2012

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA Submission	17-DEC-2012
Amendment (Response to Quality Information request (IR))	15-MAR-2013
Amendment (Response to Quality IR)	29-MAR-2013
Amendment (Response to Quality IR)	08-APR-2013
Amendment (Response to Quality IR)	14-May-2013

7. NAME & ADDRESS OF APPLICANT:

Name: ViiV Healthcare Company  
Address: GlaxoSmithKline, PO BO 13398, Bldg5  
5218 Five Moore Drive  
Reach Triangle Park, NC 27709

Representative: Martha Anne Auld, R.Ph.  
Telephone: 919-315-8319

## CMC Review Data Sheet

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

- a) Proprietary Name: Tivicay®
- b) Non-Proprietary Name: Dolutegravir Sodium
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type:
  - Submission Priority: P

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

## 10. PHARMACOL. CATEGORY: Antiviral

## 11. DOSAGE FORM: Tablets (film-coated)

## 12. STRENGTH/POTENCY: 50 mg

## 13. ROUTE OF ADMINISTRATION: Oral

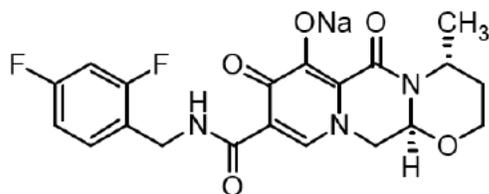
14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

Sodium (4*R*,12*aS*)-9-{{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12*a*-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate



C<sub>20</sub>H<sub>18</sub>F<sub>2</sub>N<sub>3</sub>NaO<sub>5</sub>

441.36 g/mol (dolutegravir sodium)

419.38 g/mol (dolutegravir free acid)

CMC Review Data Sheet

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4			LOA Date: 2/24/2012

<sup>1</sup> 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")

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

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	(b) (4)

**18. STATUS:**

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	17-MAY-2013	EES-PROD
Pharm/Tox	N/A		
Biopharm	Acceptable	16-MAY-2013	Deepika Arora Lakhani
LNC	N/A		
Methods Validation	Acceptable	14-MAY-2013	Michael L Trehy
DMEPA*			
EA	Categorical exclusion (see review)	19-APR-2013	Lin Qi and Maotang Zhou
Microbiology	Pending	17-MAY-2013	Steve Langille

\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 204-790

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of **TIVICAY** (dolutegravir) Tablets, 50 mg.

Draft label and labeling have adequate CMC information. Labels and labeling are pending team review as of the date of this review and will be finalized at that time.

The site recommendation from the Office of Compliance is pending as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until an Acceptable site recommendation is made by the Office of Compliance.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments

Conduct the requested (b) (4) testing for drug substance to target (b) (4) degradation, evaluate both drug substance and drug product impurities methods using these conditions, and submit the data as a Changes Being Effected in 0 Days Supplement to be filed within 6 months from the date of NDA action.

### II. Summary of CMC Assessments

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

##### (1) Drug Substance

The drug substance, dolutegravir sodium (GSK1349572A), is a white to light yellow powder, with a molecular formula of  $C_{20}H_{18}F_2N_3NaO_5$ . Dolutegravir is a new molecular entity (NME). Dolutegravir sodium is manufactured, controlled, packaged, and stability-tested at (b) (4) Shionogi Pharma Chemicals Co., Ltd., Japan. The drug substance is manufactured (b) (4). The description on manufacturing processes and controls for dolutegravir sodium, as amended, is adequate. The specification for the drug substance contains appropriate acceptance criteria for description, identification, sodium content, assay, related substances, residual solvents, water content, solid state form, particle size distribution, and heavy metals. Available batch analysis and stability data are within specifications. The six potential genotoxic impurities identified are adequately controlled by the manufacturing process to levels of no more than (NMT) (b) (4).

## Executive Summary Section

(b) (4) in the final drug substance, and are not included in the drug substance specification. The solid state form of the drug substance is verified by an identity test (b) (4) (b) (4) (b) (4) (b) (4) Data was provided to demonstrate (b) (4) does not impact drug product dissolution. The drug substance is stored (b) (4) Eighteen (18)-month long term (30 °C/65%RH and 25 °C/60% RH) and 6-month accelerated (40 °C/75% RH) stability data for three commercial scale primary stability batches of dolutegravir sodium drug substance are provided. The data supports the proposed retest period (b) (4) for the drug substance when stored up to 30 °C (86°F) and protected from light.

## (2) Drug Product

**TIVICAY** (dolutegravir) Tablets, 50 mg, is an immediate release, yellow film coated, round, biconvex tablet for oral administration. Tablets are debossed with 'SV 572' on one side and '50' on the other side. Each tablet contains 52.6 mg dolutegravir sodium, which is equivalent to 50 mg dolutegravir free acid. The formulation contains (b) (4) dolutegravir sodium, and the inactive ingredients D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film-coating contains iron oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide. All excipients comply with USP and are within levels used in other approved drug products.

Dolutegravir Tablets, 50 mg, are manufactured (b) (4)

A risk management approach was applied during process development. A few ranges/targets of variables were investigated using pilot and production scale DoE or during production scale manufacture of clinical batches. (b) (4)

are identified as critical process parameters (CPP). Fixed ranges/targets were preselected for most variables and excluded from investigation. Although these are identified as non-critical process parameters (NCPP), changes to some NCPPs could impact product quality. The applicant has agreed to assess impact on quality when NCPPs are changed. The proposed control strategy (See P.2.3.3) includes controls on drug substance attributes (See P.2.1.1), unit operation controls (See P.2.3.1), and drug product controls (See P.5.6). The drug product will be tested for Description, Identification, Content, Uniformity of Content, Drug-Related Impurities, and Dissolution, and Microbiological quality at release. The acceptance criteria are justified appropriately.

Although the HPLC test methods for drug substance and drug product were determined to be overall adequate for NDA approval by both CMC reviewers of this NDA and FDA St. Louis lab, the applicant had used a (b) (4) test condition during method development. Therefore, a post-marketing commitment was set up as described in Section I.B. to further evaluate the methods.

## Executive Summary Section

The biopharmaceutics review dated May 16, 2013 concluded the dissolution test method was discriminating. The drug substance particle size, (b) (4) design space and (b) (4) design space were supported by dissolution data. Although there was insufficient dissolution data to support the extremes of the design space, the review concluded that the dissolution acceptance criteria ( $Q = (b) (4)$  at 20 min) is likely to reject batches with dissimilar dissolution profiles.

There are no drug product changes in assay, appearance, impurities, or solid state form upon storage in the primary container during long-term (25°C/60% RH and 30°C/75% RH, accelerated (40°C/75% RH), 50°C/ambient, freeze/thaw cycle (-20°C/30°C), exposed photostability stability studies. (b) (4)

(b) (4) The available stability data support a shelf life of 24 months. Dolutegravir Tablets, 50 mg, when stored in the primary packaging [30 (b) (4) fill count] at 25°C (77°F); excursions permitted 15 to 30°C (59 to 86°F).

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

TIVICAY® is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults and children aged 12 years and older. TIVICAY Tablets may be taken with or without food. The recommended dose of TIVICAY is 50 mg administered orally once daily or twice daily. TIVICAY tablets are packaged in (b) (4) HDPE bottles with child-resistant closures, 30 (b) (4) fill counts. Only the 30 count bottle is proposed for the US market.

### C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, test methods, specifications, batch data and stability data for assuring consistent product quality of the drug substance and drug product over the storage period. The CMC information in the NDA, as amended, is sufficient to assure the identity, strength, purity, and quality of TIVICAY (dolutegravir) Tablets, 50 mg over the shelf-life granted.

Draft label and labeling have adequate CMC information. Labels and labeling are pending team review as of the date of this review and will be finalized at that time.

The site recommendation from the Office of Compliance is pending as of the date of this review.

Therefore, from the CMC perspective, this NDA is not recommended for approval until an Acceptable site recommendation is made by the Office of Compliance.

## Executive Summary Section

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

*(See appended electronic signature page)*

Lin Qi, Ph.D. and Maotang Zhou, Ph.D., CMC Reviewers, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Rapti Madurawe, Ph.D., Branch Chief, Branch V, ONDQA

**C. CC Block:** entered electronically in DARRTS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LIN QI  
05/17/2013

MAOTANG ZHOU  
05/17/2013

RAPTI D MADURawe  
05/17/2013

# Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

## Review Cover Sheet

**1. NEW DRUG APPLICATION NUMBER: 204-790**

Submission Date:	Dec 17, 2012
Mid-Cycle OND Meeting:	Mar 13, 2013
GRMP Goal Date:	May 17, 2013
OND Late-Cycle Pre-Meeting:	May 17, 2013
Late-Cycle Meeting:	June 11, 2013
PDUFA Goal Date:	Aug 17, 2013

**2. PRODUCT PROPERTIES:**

Trade or Proprietary Name:	Tivicay®
Established or Non-Proprietary Name (USAN) and strength:	Dolutegravir Each tablet contains 52.6 mg dolutegravir sodium, equivalent to 50 mg of dolutegravir
Dosage Form:	Tablets (film-coated)

**3. NAME OF APPLICANT:**

Name:	ViiV
-------	------

**4. SUBMISSION PROPERTIES:**

Review Priority :	PRIORITY (under PDUFA-V)
Property (Legal Basis):	505 (b)(1)
Responsible Organization:	DAVP

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

## **Review Information**

1. INDICATION: Treatment of HIV

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 50 mg

4. Rx/OTC DISPENSED: Rx OTC

5. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

Is this a SPOTS product? Yes No Not evaluated at time of IQA.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

**6. RELATED REVIEW DOCUMENTS:**

**a. Drug Master Files listed on 356h form:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	2/24/2012	
5 other LOAs are included for packaging components					

**b. Consults Recommended by CMC and Biopharmaceutics**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clin Pharm		X	Will be part of review team
EES	X		
Pharm/Tox		X	Will be part of review team
Methods Validation	X		
EA		X	
New Drug Micro		X	
CDRH		X	
Other ( )			NA

**c. Other Applications or Submissions to note (if any):**

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
Commercial IND		IND 75382	IND for this product
Commercial IND		IND (b) (4)	(b) (4)

**d. Previous Communications with the Applicant to note (if any):**

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
CMC PreNDA	July 25, 2012	IND 75382	Meeting Minutes
CMC EOP-2	Aug 18, 2010	IND 75382	Meeting Minutes

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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## **Overall Conclusions and Recommendations**

<b>Is the Product Quality Section of the application fileable from a CMC perspective?</b>		
Yes	No	CMC Filing Issues
X		1.

<b>Are there potential CMC review issues to be forward to the applicant with the 74 day letter?</b>		
Yes	No	CMC Comments for 74 Day Letter
	X	1.

<b>Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?</b>		
Yes	No	Biopharmaceutics Filing Issues
X		See Dr. Lakhani's separate BioPharm filing review in DARRTS

<b>Are there potential biopharmaceutics review issues to be forward to the applicant with the 74 day letter?</b>		
Yes	No	Biopharmaceutics Comments for 74 Day Letter
	X	None listed in Dr. Lakhani's filing review



**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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considered to be non-critical, and includes modest quantitative ranges for both groups. Future changes to the non-critical process parameters “will be managed under the site’s Pharmaceutical Quality System with regulatory action in conformance with post-approval regulations and guidance for minor change.” (b) (4)

A (b) (4) is used (b) (4) for three non-critical process parameters.

A rework process is described for dolutegravir sodium (b) (4) that does not meet specification. (b) (4) Justification or practical demonstration may be needed to support including a rework process in an application.

Two intermediates (b) (4) and several raw materials (b) (4) are considered to be genotoxic. They are controlled to assure a maximum level (b) (4) in the final drug substance. Information is provided in Module 2.4. Section 4.8.4, Module 2.6.6, and Module 4.2.3.7.6

The solid state form of the drug substance is verified by an identity test (b) (4) and the justification for use of a qualitative test seems reasonable.

The particle size is controlled (b) (4)

As noted by Dr. Qi, a footnote in the DS specification states that assay, related substances, and solid state form (b) (4) can be performed on (b) (4) dolutegravir sodium drug substance. Is this acceptable? Studies on equivalency of measurements (b) (4) are summarized as part of the Justification of Specifications.

Did the applicant include in the NDA the information on control of genotoxic impurities that was requested in the July 2012 PreNDA meeting? Specifically:

- GSK stated that additional studies (b) (4) have been conducted (b) (4) summarized in the PreNDA briefing package. FDA encouraged GSK to include this information in the NDA.
- GSK agreed to provide in the NDA a discussion of keeping the ppm-level analytical methods for use in change control.
- Has anything like the table of control elements for genotoxic impurities that was included in the FDA PreNDA meeting minutes been included in the NDA? This table is included in Appendix 5, below.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Drug Product**

Significant amount of process understanding is conveyed in the NDA submission.

The manufacturing processes are [redacted] (b) (4)

No bioequivalence studies have been performed for Dolutegravir Tablets, 50 mg. The formulation used in pivotal Phase III studies is identical to the commercial formulation with the following exceptions:

- The Phase III tablet is deep convex round and the commercial tablet is normal convex round.
- The Phase III tablet is film coated [redacted] (b) (4) and the commercial tablet is film coated [redacted] (b) (4)

According to the applicant, dissolution testing has confirmed the equivalence of the Phase III and commercial image tablets and is detailed in m3.2.P.2.2, Section 3.4.1.

The stability batches were made at the commercial site, with the intended commercial process. The [redacted] (b) (4) processes were at commercial scale [redacted] (b) (4)

**Table 38 Batch Details for Batches of Dolutegravir Tablets, 50 mg**

Batch Number	111284909	111284910	111284911
Ware Batch Number	R513668	R513669	R513670
Input Drug Substance Batch Number	108005 108006	108006	108007
Batch Size (Kg)	[redacted] (b) (4)		
Pack	HDPE Bottles	HDPE Bottles	HDPE Bottles
Date of Manufacture	March 2011	February 2011	February 2011
Site of Manufacture	Ware, UK	Ware, UK	Ware, UK
Use	Primary Stability	Primary Stability	Primary Stability
Scale <sup>1</sup>	Pilot	Pilot	Pilot

Note: [redacted] (b) (4)

Stability data at 25°C/60% RH and 30°C/75%RH are presented out to 12 months, along with supportive data under other conditions. A 24-mo expiry is proposed.

Is the proposal to not place the first 3 commercial lots into stability studies acceptable?

Q1A: “Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a postapproval commitment is considered unnecessary.”

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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Information is provided on both bottles of 30 (b) (4) tablets. Although only the bottles of 30 are proposed for initial marketing, the approval should cover both configurations, if both are adequately supported by data.

If supported adequately by the stability data at 30°C/75%RH, the expiration dating period could be stated to apply to either storage at USP controlled room temperature, or when stored below 30°C.

The proposed Patient Information includes a storage recommendation of:  
“Store TIVICAY at room temperature between (b) (4)” The Medical Policy reviewer may propose a narrower temperature range (20-25°C) if USP controlled room temperature remains as the recommendation in the Prescribing Information.

**QbD Elements**

My initial assessment was that, while QbD elements such as the use of DOEs to support process development were present, these did not reach the level where QbD-related input would be needed beyond the expertise within the review team. However, more in-depth evaluation by the review team identified other QbD elements. These are summarized in the Product Quality and Manufacturing Memo (PQMM), filed separately in DARRTS, and comments were added to the appropriate facilities in EES.

**Description of Facility-Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)**

*See EES for complete list of facilities related to this application.*

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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## FILING REVIEW CHECKLIST

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

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		X	See notes regarding genotoxic impurities under Drug Substance, above.

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		356h
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\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	X		25.31 (b)

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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<b>E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
13.	Does the section contain a description of the DS manufacturing process?	X		
14.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
15.	Does the section contain information on impurities?	X		
16.	Does the section contain information regarding the characterization of the DS?	X		
17.	Does the section contain controls for the DS?	X		Copy in Appendix, below
18.	Has stability data and analysis been provided for the drug substance?	X		18 months at 30°C/65%RH and 25°C/60%RH plus 6 months at accelerated  Photostability and stress (40°C/75%RH exposed, etc) are also included
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		As noted by Dr. Zhou in PQMM.
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	
21.	Does the section contain container and closure information?	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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<b>F. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
22.	Does the section contain quality controls of excipients?	X		
23.	Does the section contain information on composition?	X		Copy in Appendix, below
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		Narrative Description in Module 3 P.3.3
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
26.	Is there a batch production record and a proposed master batch record?	X		Executed batch record for Lot R513668 <div style="background-color: #cccccc; width: 100%; height: 1em; margin-bottom: 5px;"></div> A Blank Master Batch Record <div style="background-color: #cccccc; width: 100%; height: 1em; display: inline-block;"></div> is also provided in Regional Information.
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
28.	Have any Comparability Protocols been requested		X	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		HDPE bottles of 30 <div style="background-color: #cccccc; width: 1em; height: 1em; display: inline-block;"></div> tablets with induction seals and CR-closures.
30.	Does the section contain controls of the final drug product?	X		Copy in Appendix, below
31.	Has stability data and analysis been provided to support the requested expiration date?	X		12 month data on bottles of 30 <div style="background-color: #cccccc; width: 1em; height: 1em; display: inline-block;"></div> at 30°C/75%RH and 25°C/60%RH, and 6 months accelerated  Photostability and stress (40°C/75%RH exposed for 3 mo, freeze-thaw, etc) are also included  24-month expiry proposed when stored at USP controlled room temperature.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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32.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		As noted by Dr. Qi in PQMM.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	X		As noted by Dr. Qi in PQMM.

<b>G. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	Is there a methods validation package?		X	A separate MV package is not needed for an electronic submission.

<b>H. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?			NA

<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
36.	Has the draft package insert been provided?	X		Includes: Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium)
37.	Have the immediate container and carton labels been provided?	X		Bottle only; Copy in Appendix, below
38.	Does section contain tradename and established name?	X		

<b>FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
39.	<b>ARE THE PRODUCT QUALITY SECTIONS OF THE APPLICATION FILEABLE?</b>	X		
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable.
41.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Not applicable.

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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42.	Are there any potential review issues identified?		X	
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**ONDQA Initial Quality Assessment (IQA) and Filing Review  
For Pre-Marking Applications**

## **REVIEW AND APPROVAL**

*See appended electronic signature page*

Stephen Miller, Ph.D.

CMC-Lead

Division of Pre-Marketing Assessment II, Branch V

Office of New Drug Quality Assessment

*See appended electronic signature page*

Rapti Madurawe, Ph.D.

Branch Chief

Division of Pre-Marketing Assessment II, Branch V

Office of New Drug Quality Assessment

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Appendix 1. Composition of Drug Product**

**Table 1      Composition of Dolutegravir Tablets, 50 mg**

Component	Quantity (mg/tablet)	Function	Reference to Standard <sup>1</sup>		
<b>Intragranular excipients</b>					
Dolutegravir Sodium <sup>2</sup>	52.6	Active	Supplier		
D-Mannitol <sup>3</sup>	(b) (4)	(b) (4)	USP		
Microcrystalline Cellulose			USNF		
Povidone K29/32			USP		
Sodium Starch Glycolate			USNF		
(b) (4)			USP		
(b) (4)			USNF		
Sodium Stearyl Fumarate			USNF		
(b) (4)			-		
<b>Film coating</b>			(b) (4)	(b) (4)	Supplier
(b) (4)			(b) (4)	(b) (4)	USP
<b>Total Coated Tablet Weight</b>	(b) (4)	(b) (4)	-		

**Note:**

1. Details of the specifications of the active ingredient are provided in [m3.2.S.4.1](#). Details of the specifications of the excipients are provided in [m3.2.P.4](#).

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Appendix 2. DP Specification (from QOS)**

Test	Acceptance Criteria	Module 3 Method Location/Link
Description	Yellow, round, biconvex tablets debossed with 'SV 572' on one side and '50' on the other side.	<a href="#">m3.2.P.5.2 Analytical Procedures_Description</a>
Identification of Dolutegravir by HPLC <sup>1</sup>  by UV <sup>1</sup>	(b) (4)	<a href="#">m3.2.P.5.2 Analytical Procedures_Determination of Content, Identification, and Uniformity of Content in Dolutegravir Tablets, 50 mg by HPLC</a>  <a href="#">m3.2.P5.2 Analytical Procedures_Determination of Identification and Dissolution of Dolutegravir Tablets, 50 mg by UV Spectroscopy</a>
Dolutegravir Content by HPLC (% Label Claim)		<a href="#">m3.2.P.5.2 Analytical Procedures_Determination of Content, Identification, and Uniformity of Content in Dolutegravir Tablets, 50 mg by HPLC</a>
Drug Related Impurities Content by HPLC (% area) <sup>2,3,4</sup> Any unspecified degradation product Total degradation products		<a href="#">m3.2.P.5.2 Analytical Procedures_Determination of Drug-Related Impurities in Dolutegravir Tablets, 50 mg by HPLC</a>
Uniformity of Content by HPLC (% Label Claim) <sup>1</sup>		<a href="#">m3.2.P.5.2 Analytical Procedures_Determination of Content, Identification, and Uniformity of Content in Dolutegravir Tablets, 50 mg by HPLC</a>
Dissolution by UV (% Dolutegravir Released)		<a href="#">m3.2.P.5.2 Analytical Procedures_Determination of Identification and Dissolution of Dolutegravir Tablets, 50 mg by UV Spectroscopy</a>

Notes:

(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Appendix 3. DS Specification**

Test <sup>1</sup>	Acceptance Criteria	Module 3 Method Location/Link
Description	White to light yellow powder	<a href="#">m3.2.S.4.2 Description</a>
(b) (4)		
Note: (b) (4)		

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Appendix 4. Container and Carton Labels**



**No carton labels in Module 1**

**ONDQA Initial Quality Assessment (IQA) and Filing Review  
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**Appendix 5. Table Summarizing Control of Genotoxic Impurities from PreNDA Meeting Minutes (July 25, 2012)**

**Table 3      Control of Genotoxic Impurities**



(b) (4)

**Notes:**

LOD = Limit of Detection; LOQ = Limit of Quantitation

(b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STEPHEN MILLER

02/21/2013

This NDA is recommended for filing from the CMC perspective.

RAPTI D MADURAWA

02/21/2013