CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211994Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211994
Review #1

Drug Name/Dosage Form	Dolutegravir and Lamivudine Tablets
Strength	50 mg / 300 mg (Fixed Dose Combo)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ViiV Healthcare
US agent, if applicable	GSK

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	Oct 18, 2018	All
Amendment	Nov 7, 2018	Quality
Amendment	Jan 16, 2019	Quality
Amendment	Jan 25, 2019	Quality
Amendment	Feb 26, 2019	Quality
Amendment	Mar 1, 2019	Quality
Amendment	Mar 4, 2019	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Kabir Shahjahan	Su (Suong) Tran
Drug Product & Labeling	Peter Guerrieri	Stephen Miller
Process / Facility / Microbiology	Satheesh Podaralla	Steven Frisbee
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
Various	Type III & IV	See DP review				
	Other	N/A				

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Multiple	IND 127475	IND for this product

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

Executive Summary

I. Recommendations and Conclusion on Approvability

NDA 211994 is recommended for **APPROVAL** from the Product Quality perspective.

II. Summary of Quality Assessments

A. Product Overview

DOVATO, is a fixed dose combination of dolutegravir, an integrase strand transfer inhibitor (INSTI), and lamivudine, a nucleoside analogue reverse transcriptase inhibitor (NRTI). The individual layers of this bilayer tablet are (b) (4)

Proposed Indication(s) including Intended Patient Population	Indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults.
Duration of Treatment	Chronic, unless resistance develops.
Maximum Daily Dose	One tablet (50 mg dolutegravir and 300 mg lamivudine) daily.
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance:
The CMC information of the drug substance **dolutegravir sodium** is cross referenced to NDA 204790 (TIVICAY Tablet, 50 mg). Both NDAs have the same applicant ViiV Healthcare. The approved referenced NDA 204790 has four manufacturing sites for dolutegravir sodium. Three of these four manufacturing sites use synthetic route (b) (4), and one manufacturing site uses synthetic route (b) (4). In the referenced NDA, FDA approved both the routes and all four manufacturing sites for dolutegravir sodium. The specifications for dolutegravir sodium from route (b) (4) and route (b) (4) are provided in the NDA 211994 submission and are the same as in the approved referenced NDA 204790. The batch analyses data of four batches of dolutegravir sodium from route (b) (4) are provided in NDA 211994, and batch analyses data in the referenced NDA 204790 demonstrate acceptable comparability between route (b) (4) and route (b) (4). The particle size data from routes (b) (4) and (b) (4) are comparable and of ~(b) (4) µm. The particle size is monitored with an acceptance criteria of $X_{90} \leq$ (b) (4) um in the specification for (b) (4) dolutegravir sodium drug substance from both the routes. All batches meet the XRPD identity test for solid-state (b) (4). There are some differences in the impurity profile, but total impurity levels are low and comparable: (b) (4)% for Route (b) (4) and (b) (4)% for Route (b) (4).

The CMC information of drug substance, **lamivudine**, is cross-referenced to the approved NDA 20564 (EPIVIR Tablet, 300 mg). Both NDAs have the same applicant ViiV Healthcare. The specification provided in NDA 211994 is the same as in the approved referenced NDA 020564. The batch analyses data for supportive stability batches and clinical batches provided in the submission conform to the drug substance lamivudine specification. For additional details, see Kabir Shahjahan 's Drug Substance review, below.

Drug Product

The drug product is a fixed dose combination, immediate release bilayer tablet for oral administration containing 52.6 mg dolutegravir sodium, which is equivalent to 50 mg dolutegravir (free acid), and 300 mg lamivudine. The tablets are packaged in an opaque, white, round, high density polyethylene (HDPE) bottle of 30 tablets, with a (b) (4) child-resistant closure that includes (b) (4) induction seal liner with no desiccant. The proposed shelf life of 24 months at storage below 30°C is adequately supported by 12 months of stability batch results. No significant trends were observed at the 30°C/75% RH storage condition over 12 months. A ^{19}F solid-state NMR study with drug product stored in the commercial pack for 6 months at 25°C/60% RH, 6 months at 40°C/75% RH, and 9 months at 30°C/75% RH, indicated that the dolutegravir sodium (b) (4) is maintained, mitigating risk for conversion of dolutegravir sodium to the free form during manufacture or over the shelf life. Additional XRPD results, discussed in the review, mitigate the risk for conversion of dolutegravir sodium to (b) (4). For additional details, see Peter Guerrieri's Drug Product review, below.

Manufacturing

Proposed NDA product is a bilayer tablet indicated for complete regimen for the treatment of HIV infection. (b) (4)

Minor process deficiencies were addressed by the firm and the currently proposed in-process controls are adequate. Based on manufacturing risk identified in the NDA review, low complexity of the manufacturing process, scale up performed, and the use of on-site controls to ensure CQAs (including the robustness of (b) (4) control), no pre-approval inspection at the drug product manufacturing site was recommended. An Overall Manufacturing Facility Recommendation of Approve was entered on 03/01/2019. For additional details, see Satheesh Podaralla's Manufacturing Integrated Assessment, below.

Biopharmaceutics:
The proposed dissolution method [USP apparatus II (Paddle) at 65 rpm; 900 mL of 0.01 M phosphate buffer, pH 6.8, with 0.20% w/v SDS at 37°C] and dissolution acceptance criteria of Q = (b) (4)% at 20 minutes for dolutegravir, and Q = (b) (4)% at 15 minutes for lamivudine are acceptable. The formulation and manufacturing site of the drug product used in the pivotal BE clinical study is reported to be the same as that of the proposed commercial drug product, except for the film coating. The provided complete dissolution profile data support the film coating change between the clinical drug product and the proposed commercial drug product. For additional details, see Qi Zhang's Biopharmaceutics review, below.

C. Special Product Quality Labeling Recommendations (NDA only)

The recommendations in Peter Guerrieri's OPQ Labeling review, below, have been conveyed to OND.

D. Final Risk Assessment (see Attachment)

Stephen Miller

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Comments: ATL for NDA 211994

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LABELING

IQA Review Guide Reference

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Adequate
Dosage form, route of administration	Adequate
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Adequate

2. *Section 2 Dosage and Administration*

DOVATO is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no known substitutions associated with resistance to the individual components of DOVATO.

2 DOSAGE AND ADMINISTRATION

2.1 (b) (4)

Perform pregnancy testing before initiation of DOVATO in (b) (4) of childbearing potential [see Warnings and Precautions (5.6), Use in Specific Populations (8.1, 8.3)].

2.2 Recommended Dosage

DOVATO is a fixed-dose combination product containing 50 mg of dolutegravir and 300 mg of lamivudine. The recommended dosage regimen of DOVATO in adults is one tablet taken orally once daily with or without food.

2.3 Recommended Dosage with Certain (b) (4)

The dolutegravir dose (50 mg) in DOVATO is insufficient when coadministered with (b) (4) listed in Table 1 that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended.

Table 1. Dosing Recommendations for DOVATO with Coadministered (b) (4)

Coadministered Drug	Dosing Recommendation
Carbamazepine, rifampin	(b) (4) An additional dolutegravir 50-mg tablet, separated by 12 hours from DOVATO, should be taken.

2.4 Not Recommended (b) (4)

Because DOVATO is a fixed-dose tablet and cannot be dose adjusted, DOVATO is not recommended in:

- patients with creatinine clearance less than 50 mL per minute *[see Use in Specific Populations (8.6)]*.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A

3. *Section 3 Dosage Forms and Strengths*

DOVATO tablets are oval, biconvex, white, film-coated tablets, debossed with "SV 137" on one face. Each tablet contains 50 mg of dolutegravir and 300 mg of lamivudine. *[see Description (11)]*.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Adequate
Strengths: in metric system	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Adequate

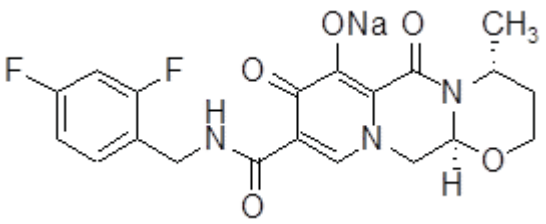
4. *Section 11 Description*

DOVATO is a fixed-dose combination tablet containing dolutegravir (as dolutegravir sodium), an INSTI, and lamivudine (also known as 3TC), an NRTI.

DOVATO tablets are for oral administration. Each film-coated tablet contains the active ingredients 50 mg of dolutegravir (equivalent to 52.6 mg dolutegravir sodium) and 300 mg of lamivudine and the inactive ingredients magnesium stearate, mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, sodium stearyl fumarate. The tablet film-coating contains the inactive ingredients hypromellose, polyethylene glycol, titanium dioxide.

Dolutegravir

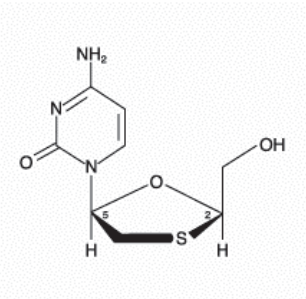
The chemical name of dolutegravir sodium is sodium(4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g/mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Lamivudine

The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 g/mol. It has the following structural formula:



Lamivudine is a white to off-white crystalline solid and is soluble in water.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Adequate
Dosage form and route of administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Adequate.
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A

5. ***Section 16 How Supplied/Storage and Handling***

Each DOVATO tablet contains 50 mg of dolutegravir as dolutegravir sodium and 300 mg lamivudine and is an oval, biconvex, white, film-coated tablet, debossed with "SV 137" on one face.

Bottle of 30 tablets with child-resistant closure NDC 49702-246-13.
Store below 30°C (86°F).

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate.
Available units (e.g., bottles of 100 tablets)	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate.
Special handling (e.g., protect from light)	NA
Storage conditions	Adequate.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate (included in section 17)

Reviewer's Assessment of Package Insert: ***Adequate***

The Prescribing Information complies with all regulatory requirements from a CMC perspective.

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

[redacted]

2. *Carton Label*

No carton is included in the submission.

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate.	N/A
Dosage strength	Adequate.	N/A
Net contents	Adequate.	N/A
"Rx only" displayed prominently on the main panel	Adequate.	N/A
NDC number (21 CFR 207.35(b)(3)(i))	Adequate.	N/A
Lot number and expiration date (21 CFR 201.17)	Adequate.	N/A
Storage conditions	Adequate.	N/A
Bar code (21CFR 201.25)	Adequate.	N/A
Name of manufacturer/distributor	Adequate.	N/A
And others, if space is available	N/A	N/A

Reviewer's Assessment of Labels: ***Adequate***
The labels comply with all regulatory requirements from a CMC perspective.

Updates to the label during the review cycle included:

a) A statement was added to the bottle label indicating the package is child-resistant.
b) The applicant was requested to provide written varication that the child-resistant package meets the Consumer Product Safety Commission's standards under 16 CFR 1700. A certificate of compliance verifying compliance was included in the amendment dated 02/26/2019.

List of Deficiencies: None

Overall Assessment and Recommendation:

Primary Labeling Reviewer Name and Date:

Pete Guerrieri, Ph.D.; Branch 3; Division of New Drug Product I. 07Mar2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Stephen P. Miller, Ph.D.; Branch 3; Division of New Drug Product I

Peter Guerrieri

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Stephen Miller

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NDA: 211994
Submission Type: 505(b)(2)
Drug Product Name/Strength: DOVATO (dolutegravir and lamivudine) tablets, 50 mg/300 mg (Two-drug Fixed Dose Combination)
Applicant Name: ViiV (GSK as agent)
Dosage Form: Immediate Release Tablets
Route of Administration: Oral (recommended dose: one tablet once daily with or without food)
Intended for Use: Treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults
Cross Referenced NDAs:
NDA 204790, TIVICAY (dolutegravir) Tablets, Approved 12 August 2012; ViiV
NDA 020564, EPIVIR (lamivudine) Tablets, Approved 17 November 1995; ViiV
NDA 020596, EPIVIR (lamivudine) Oral Solution, Approved 17 November 1995, ViiV
NDA 205551, TRIUMEQ (abacavir, dolutegravir and lamivudine) tablets, Approved 22 August 2014; ViiV
Primary Reviewer: Qi Zhang, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D.

REVIEW SUMMARY

This Biopharmaceutics review focused on **1)** the evaluation of the adequacy of the proposed dissolution method and acceptance criteria for the proposed drug product, and **2)** bridging throughout product development.

1) **Dissolution Method and Acceptance Criteria:** The proposed dissolution method [USP apparatus II (Paddle) at 65 rpm; 900 mL of 0.01 M phosphate buffer, pH 6.8, with 0.20% w/v SDS at 37°C] and dissolution acceptance criteria of Q = (b)(4)% at 20 minutes for dolutegravir, and Q = (b)(4)% at 15 minutes for lamivudine are acceptable.

USP Apparatus	Speed (RPMs)	Medium	Volume/Temp	Acceptance criteria	
II (Paddle, with sinkers)	65	0.01M phosphate buffer, pH 6.8, with 0.20% w/v SDS	900 mL/37°C	lamivudine	NLT (b)(4)% (Q) in 15 minutes
				dolutegravir	NLT (b)(4)% (Q) in 20 minutes

2) **Bridging Throughout Product Development:** The formulation and manufacturing site of the drug product used in the pivotal BE clinical study is reported to be the same as that of the proposed commercial drug product, except for the film coating. The provided complete dissolution profile data support the film coating change between the clinical drug product and the proposed commercial drug product.

BIOPHARMACEUTICS REVIEW RECOMMENDATION*:*

From the Biopharmaceutics perspective, NDA 211994-ORIG-1 for DOVATO (dolutegravir and lamivudine) tablets, 50 mg/300 mg is **ADEQUATE** and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0000 (1)	10/18/2018	Original Submission
0011(11)	1/25/2019	Response to Information Request Dated 1/14/2019

BCS DESIGNATION

A BCS designation is not requested, nor required. The Applicant claims that dolutegravir is a BCS class II drug and lamivudine is a BCS Class III drug.

Solubility: Dolutegravir has pH independent solubility and exhibits low solubility (less than 60 µg/mL) across the physiological pH range (pH 1-7) at 25°C (**Figure 1**). Since a solubility of 167 µg/mL would be required to provide sink conditions for the maximum strength dose of 50 mg dolutegravir in 900 mL, there is need to add surfactant in the dissolution medium to ensure adequate drug release. Lamivudine exhibits high solubility with a range of 75.7-145.8 mg/mL across the gastrointestinal pH range at 25°C (**Table 1).**

Figure 1: Solubility vs. pH for Dolutegravir Sodium (GSK1349572A)

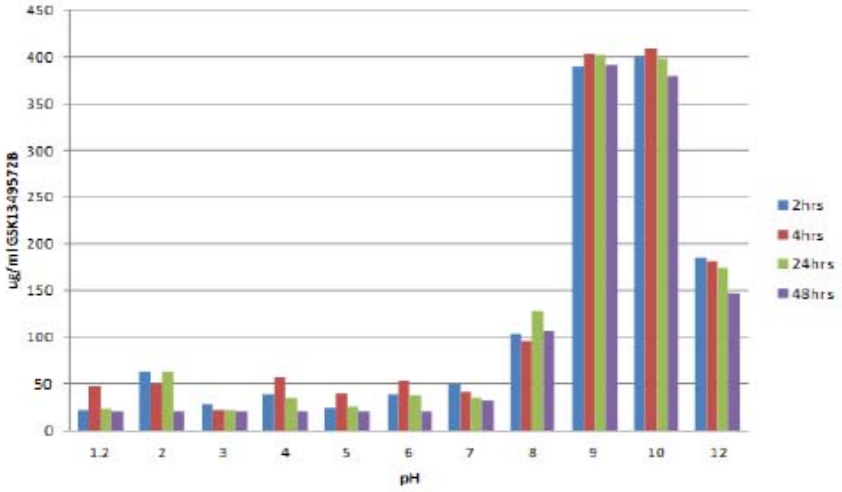


Table 1: Solubility vs. pH for Lamivudine

Measured pH	Solubility (mg/mL)
1.2	145.8
4.5	169.7
6.8	75.7

Permeability: Not reported.

DISSOLUTION

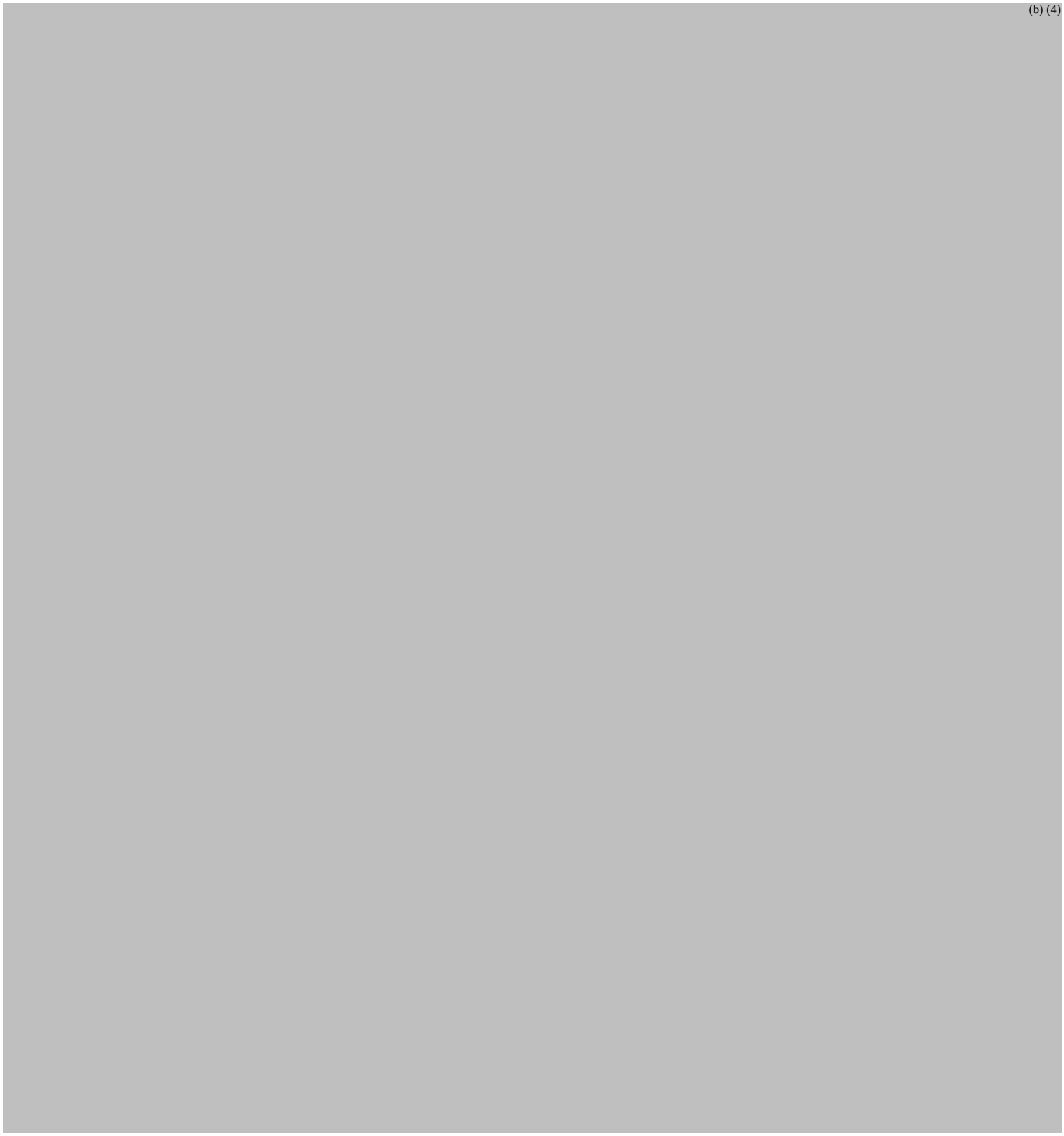
Proposed Dissolution Method and Acceptance Criteria:

USP Apparatus	Speed (RPMs)	Medium	Volume/Temp	Acceptance criteria	
II (Paddle, with sinkers)	65	0.01M phosphate buffer, pH 6.8, with 0.20% w/v SDS	900 mL/37°C	lamivudine	NLT (b) (4)% (Q) in 15 minutes
				dolutegravir	NLT (b) (4)% (Q) in 20 minutes

Dissolution Method Development:

(b) (4)

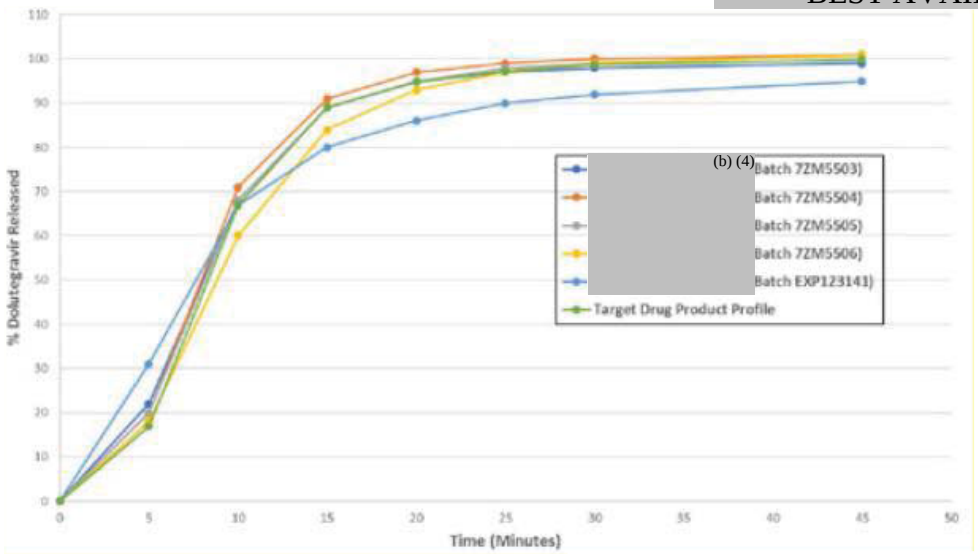
(b) (4)



Discriminating Capability of the Dissolution Method:

The proposed dissolution method can discriminate toward critical manufacturing process parameters of (b) (4) for dolutegravir (**Figure 4**); however, all batches will pass Q= (b) (4) % at 20 minutes

Figure 4: Mean Dissolution Profiles for Dolutegravir of Dolutegravir/lamivudine Tablets Manufactured Using Different Dolutegravir (b) (4) Conditions Using the Proposed Dissolution Method



- *Target Drug Product: Bio-batch 7ZM1988* (b) (4) *;*
- *Batch EXP123141* (b) (4) *did not pass the MICRP (Model Independent Multivariate Confidence Region Procedure) test at the 10% similarity limit, therefore, supporting the discriminating ability of the proposed dissolution method for dolutegravir.*

Justification of The Proposed Dissolution Method for Lamivudine:

In the Applicant's responses (submission date 1/25/2019) to the Biopharmaceutics Information Request Comments (IR letter dated 1/14/2019) recommending a separate dissolution medium without surfactant for lamivudine, the Applicant provided the following points to justify the use of a single dissolution method:

1. Lamivudine exhibits high solubility (**Table 1**). The lowest solubility of 75.7 mg/mL would provide complete dissolution in 4 mL aqueous solution for the 300 mg lamivudine dose.
2. Lamivudine exhibits very rapid, consistent dissolution irrespective of the dissolution medium, volume or agitation speed. At all pHs (pH 1.2, pH 4.5 and pH 6.8) > 85% lamivudine was dissolved by 15 minutes per the dissolution method in the 2018 BCS I/III dissolution guidance (**Figure 5**). Similar dissolution profiles with > 85% lamivudine dissolved are obtained in pH 1.0, 4.5 and 6.8 using the proposed dissolution conditions with and without surfactant (**Figures 6 and 7**).
3. A tight specification Q = (b) (4) % at 15 minutes has been applied for lamivudine, compared to the recommended 30 minutes per the dissolution method in the 2018 BCS I/III dissolution guidance.
4. The solubility and dissolution data are actually supportive of disintegration being used in lieu of a dissolution test according to ICH Q6A. Application of a single harmonized dissolution method for simultaneous determination of the dissolution rate of both active components provides significant operational and sustainability advantages.

Figure 5: Dissolution of Lamivudine for the Bio-batch In Different pH Media With No Surfactant Using The Dissolution Method In 2018 BCS I/III Dissolution Guidance (USP Apparatus II at 50 rpm in 500 mL medium)

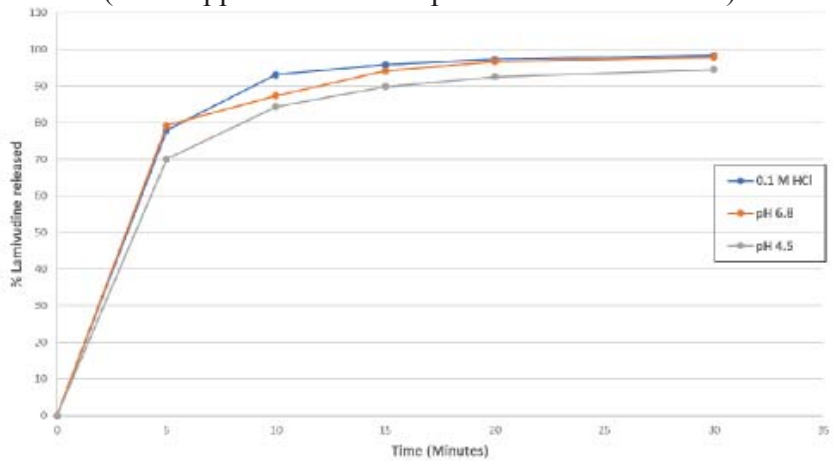


Figure 6: Dissolution of Lamivudine for the Bio-batch in Different pH With No Surfactant Using the Proposed Dissolution Conditions (USP Apparatus II at 65 rpm in 900 mL medium)

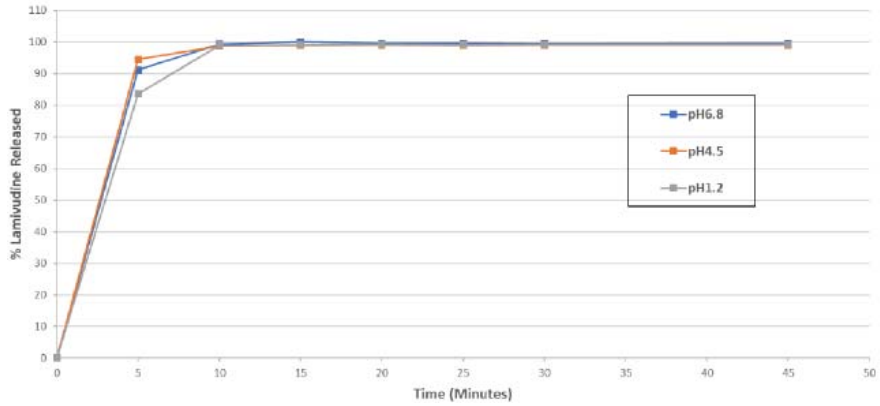
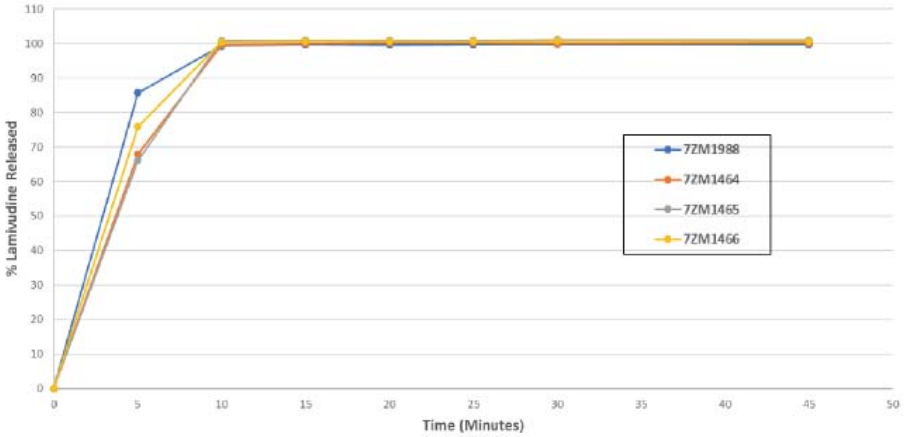


Figure 7: Dissolution of Lamivudine For The Biobatch And Registration Stability Batches With 0.2% Surfactant Using The Proposed Dissolution Conditions
(USP Apparatus II at 65 rpm in 900 mL 0.01 M phosphate buffer pH 6.8)



This Reviewer noted that the relative bioavailability of EPIVIR (lamivudine) Tablets when compared to lamivudine oral solution has no difference in adults (refer to the approved US package insert for EPIVIR (lamivudine) oral solution, NDA 20596), suggesting insignificant effect of tablet dissolution on drug absorption compared to oral solution.

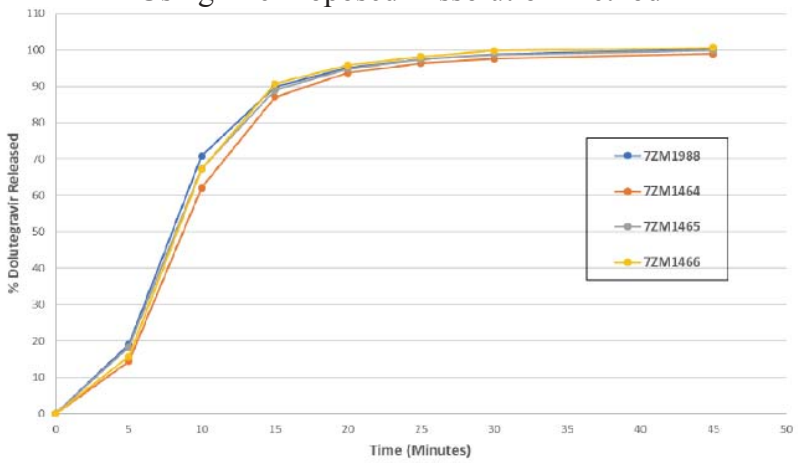
Validation for Dissolution Method:
The proposed dissolution method has been validated for precision and dissolution robustness (with regards to SDS concentration, phosphate concentration in dissolution medium, pH of dissolution medium, and paddle speed), at the proposed sampling time point 20 minutes for dolutegravir and 15 minutes for lamivudine. For the evaluation of the adequacy of the validation of the analytical HPLC method (including the HPLC method used for dissolution testing), refer to the Drug Product Review.

Reviewer's Assessment:

The Applicant's justifications for their proposed single dissolution method are acceptable. The proposed dissolution method is validated and is considered adequate for the quality control for both APIs of the proposed dolutegravir and lamivudine tablets, based on the availability of sufficient sink conditions and complete dissolution, as well as, discriminating ability of the method towards critical manufacturing process parameters of (b) (4) *for the low solubility dolutegravir.*

Dissolution Acceptance Criteria:
Complete dissolution profile data for the biobatch (7ZM1988) and three registration stability batches (7ZM1464, 7ZM1465, 7ZM1466) with > 90% mean dissolution in 20 minutes for dolutegravir and 15 minutes for lamivudine fully support the proposed NLT (b) (4) % (Q) at 20 minutes for dolutegravir and 15 minutes for lamivudine. All batches can pass S1 test at release (**Figures** 7 and 8).

Figure 8: Dissolution of Dolutegravir For The Biobatch and Registration Stability Batches Using The Proposed Dissolution Method



It is noted that, though the mean dissolution values are > 85% at 15 minutes for dolutegravir, two registration batches need S2 test (i.e., the minimum individual dissolution values are (b) (4)% and (b) (4)% at 15 minutes). In addition, a minimum time point of 20 minutes is indicated to meet a Q = (b) (4)% limit based on the resulting lower f_2 bound values for the clinical batches. Taking into consideration the low solubility and T_{max} (2-3 hours) of dolutegravir, this reviewer considers the proposed Q= (b) (4)% at 20 minutes to be adequate for the quality control of the proposed drug product for dolutegravir.

Reviewer's Assessment: **Adequate**

The proposed dissolution acceptance criteria of Q = (b) (4)% at 20 minutes for dolutegravir, and Q = (b) (4)% at 15 minutes for lamivudine are acceptable.

BRIDGING THROUGHOUT PRODUCT DEVELOPMENT

Drug Substance

During the review cycle, issue arose as to whether bridging is need for the low solubility drug dolutegravir because there are three proposed commercial manufacturing sites with two routes of synthesis for dolutegravir, and the biobatch was manufactured by the DS from (b) (4). Through discussion with the CMC reviewers, a decision has been made that the bridging of these different DS sites was unnecessary, since all the sites were previously approved, and the proposed DS specifications are the same compared to the specification provided in the referenced approved NDA 204790. The solid-state form and particle size have the same acceptance criteria for DS made by the two synthetic routes (b) (4)), in addition, batch release data are comparable for the different DS sources. Refer to the Drug Substance and Drug Product Reviews for additional information.

Drug Product

Both a monolayer (Product Code AH) and bilayer (Product Code AK, biobatch 7ZM1988) formulation of dolutegravir/lamivudine tablets were used in the pivotal BE clinical study, comparing the FDC tablets to co-administration of the separate tablet formulations of dolutegravir 50 mg and lamivudine 300 mg (Study 204994) (**Figure 9**). Based on the PK results from Study 204994, the bilayer formulation AK was selected as the commercial formulation. The final proposed commercial formulation (Product Code AM) is the same as AK, except the only difference in the film coating level: (b) (4)% w/w in AK and (b) (4) % w/w in AM (**Table 4**). The formulation change between AK and AM is similar to a SUPAC Level (b) (4). The provided dissolution profiles with > 85% dissolution for both APIs for the biobatch 7ZM1988 (AK) and the three primary stability batches (AM) support the film coating change between the clinical and the proposed commercial drug product. It is noted that the Phase 3 clinical efficacy studies used single entity (SE) DPs. It is also noted that the bilayer formulation has an 32% higher Cmax than the co-administration of SE for lamivudine; refer to the Clinical Pharmacology (CP) Review for the determination of the adequacy of PK bridging between the bilayer formulation and the combination of the SE tablets.

Figure 9: Schematic Diagram of Oral Formulations Used during the Clinical Development

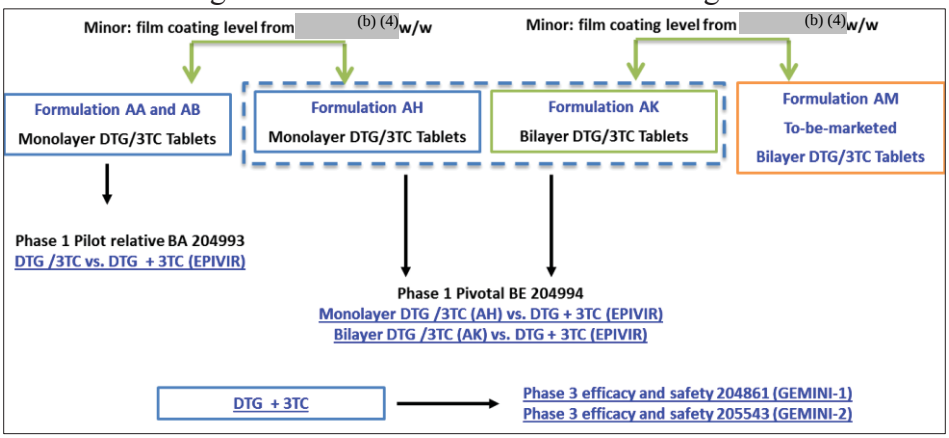


Table 2: Bilayer DTG/3TC Tablet Formulations Used in the BE and Primary Stability Studies

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Component	Quantity (mg/tablet)	
	Bilayer DTG/3TC Tablets	Bilayer DTG/3TC Tablets
Formulation Product Code	AK	AM
Study	BE - 204994	Primary Stability

(b) (4)

Reviewer's Assessment: ADEQUATE

The formulation of the drug product used in the pivotal BE study is reported to be the same as that of the proposed commercial drug product, except for the film coating. The provided complete dissolution data support the coating change between the clinical and the proposed commercial drug product. The manufacturing process and manufacturing site of the drug product batches used in the clinical and stability studies are the proposed commercial manufacturing process and site.

BIOWAIVER REQUEST

A biowaiver is not requested nor required for this NDA. There is only one fixed dose combination strength proposed, 50 mg/300 mg, and the Applicant conducted the clinical BE study between the proposed bilayer formulation and the co-administration of the separate tablet formulation of dolutegravir 50 mg and lamivudine 300 mg (BE Study 204994).

CONCLUSION and RECOMMENDATION

From the Biopharmaceutics perspective, NDA 211994-ORIG-1 for DOVATO (dolutegravir and lamivudine) tablets, 50 mg/300 mg is **ADEQUATE** and recommended for **APPROVAL**.

BIOPHARMACEUTICS INFORMATION REQUEST (IR)

IRs dated 1/14/2019:

1. To support the discriminating ability of the proposed dissolution method for dolutegravir, provide complete dissolution profile data (n=12, individual, mean, RSD, and profiles) associated with the Figures 12, 14, and 16 presented in 3.2.P.5.3 (Analytical Development). Clearly specify the target drug product batch and include results of a statistical similarity test (e.g. f2 test) for the dissolution profile comparisons.
2. Based on the provided dissolution data, a separate dissolution test using medium without surfactant is recommended for lamivudine.
3. It is noted that you only provided mean dissolution data collected at 20 minutes for dolutegravir and 15 minutes for lamivudine for your proposed DTG/3TC tablets in Table 3 presented in P.5.6 justification of specifications. Provide complete dissolution profile data (n=12, individual, mean, RSD, and profiles) for dolutegravir and lamivudine using two separate methods (with surfactant for dolutegravir and without surfactant for lamivudine) at each sampling time points e.g. 5, 10, 15, 20, 25, 30, and 45 minutes for the biobatch and the three primary stability batches. Indicate the age of the batch and the storage conditions at the time of dissolution testing.
4. Submit all the requested complete dissolution profile data in ".xlsx" format.

In the Applicant's responses (submission date 1/25/2019) the Applicant provided an acceptable justification for the use of a single dissolution method.

Qi Zhang

Digitally signed by Qi Zhang
Date: 3/07/2019 01:12:21PM
GUID: 547e178000007695c91eb10380b07939

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 3/07/2019 01:27:00PM
GUID: 50743ccc000031928b54eba1769a5df9

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Dolutegravir and Lamivudine Tablets (NDA 211994)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations/ Comments**
Assay, Stability		**L**	(b) (4)	Acc	
Physical stability (solid state)	Low- solubility dolutegravir Na	**M**		Acc	
Content uniformity	Dolutegravir Na at (b) (4)	**M**		Acc	
Microbial limits		**L**		Acc	
Dissolution – BCS Class II & IV	Low- solubility dolutegravir Na	**M**		Acc	
Patient Use Considerations	Un-scored tablet; no instructions for dispersing in water	**L**		Acc	

Stephen Miller

Digitally signed by Stephen Miller
Date: 3/29/2019 08:17:45AM
GUID: 508da7210002a000609476bbecd040f0
Comments: ATL for NDA 211994