

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211284Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

**NDA 211284
Review #1**

Drug Name/Dosage Form	Temixys (lamivudine and tenofovir disoproxil fumarate) Tablets
Strength	300 mg/300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Celltrion, Inc.
US agent, if applicable	ELc Group/ Ms. Jimmy Han

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	1/15/2018	All
Quality Amendment	4/6/2018	Drug Product
Quality Amendment	5/21/2018	Process
Quality Amendment	6/25/2018	Drug Product/ Facility/Drug Product
Quality Amendment	6/27/2018	Drug Substance/ Drug Product
Quality Amendment	7/12/2018	Drug Product/ Process
Quality Amendment	7/25/2018	Drug Product

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Mohd Shahjahan Kabir	Charles Jewell
Drug Product & Labeling	Yong Wang	Balajee Shanmugam
Process	Steven Frisbee	Upinder Atwal
Microbiology	Steven Frisbee	Upinder Atwal
Facility	Steven Frisbee	Derek Smith
Biopharmaceutics	Parnali Chatterjee	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
(b) (4)	Type II	(b) (4)	Lamivudine Drug Substance	Adequate	Aug 3, 2018 (M. Kabir)	Filed under MF (b) (4) Orig-1
	Type II		Tenofovir DF Drug Substance	Adequate	Oct 13, 2016 (Ying Lin)	Filed under MF (b) (4) GL-1
Various	Type III)	See DP review				
Various	Type IV	See DP review				

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA's for similar products from other Applicants are listed in this public database:	http://www.fda.gov/InternationalPrograms/PEPFAR/ucml19231.htm	

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 211284 is recommended for final **APPROVAL** from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

Temixys is a two-drug fixed dose combination tablet containing 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. Multiple versions of this product from different applicants have received tentative approval under the PEPFAR program. Because the patents for both actives have now expired, this NDA will be the first application for this combination to receive final approval, allowing marketing in the US.

Proposed Indication(s) including Intended Patient Population	In combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients [redacted] (b) (4) weighing at least 35 kg.
Duration of Treatment	Chronic
Maximum Daily Dose	One tablet once daily with or without food.
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance:

The DMFs for both actives are currently adequate. See the DMF table on the previous page for details.

Both active ingredients have high solubility by the Biopharmaceutics Classification System. The manufacturing process for lamivudine drug substance consistently produces [redacted] (b) (4)

[redacted] which is included in the applicant's drug substance specification.

For additional details, see Mohd Kabir's Drug Substance review, below.

Drug Product:

Temixys (lamivudine and tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg are white oblong shaped, film-coated tablets debossed with “C 0” on one side and plain on the other side. Compendial excipients that were selected for the formulation were confirmed by compatibility studies. Optimization studies were carried out to select the level of the disintegrant, (b) (4)

The drug product specification is comprehensive and appropriate, and includes monitoring by (b) (4) lamivudine and (b) (4) tenofovir DF. Because of the sensitivity of tenofovir DF (b) (4)

Stability data out to 6 month at 30°C/75%RH adequately support the 24-month expiration dating period when the product is stored under the following conditions: *Store below 30°C (86 °F). Keep bottles tightly closed to protect from moisture. Dispense and store only in original bottle.* The stability data supports the quality of three packaging configurations: bottles of 30, 60 and 100 count, each with desiccant, induction seal and child-resistant closure. The June 25, 2018 amendment clarified that all three configurations will be available for the PEPFAR market, but that only the 30-count bottle will be commercialized in the US.

For additional details, see Yong Wang’s Drug Product review, below.

Process:

(b) (4)

(b) (4)

Biopharmaceutics:

The proposed dissolution method (USP Apparatus II at 50 rpm paddle speed in 900 mL 0.1 N HCl) was determined to exhibit limited discriminatory power. In response to FDA recommendations, the Applicant agreed to (b) (4) dissolution acceptance criterion to $Q = \frac{(b) (4)}{(4)}\%$ in 20 minutes for batch release and stability testing of Temixys tablets.

No bridging is necessary between the bio-batch (CBAU002F) and the commercial drug product because there are no differences in the formulation, manufacturing process, manufacturing site, or drug product image/coating/debossing.

For additional details, see Parnali Chatterjee's Biopharmaceutics review, below.

Facilities:

Following review of the inspectional histories of the drug substance and drug product manufacturing facilities, a Preapproval inspection performed for the lamivudine drug substance manufacturing facility, and suitable responses to information requests, all listed facilities for NDA 211284 are found to be acceptable for their proposed manufacturing and/or testing operations. Therefore, there are no significant outstanding manufacturing or facility risks that prevent approval of this application. A recommendation to Approve was entered for the Submission Overall Manufacturing Facility Status in Panorama on Aug 31, 2018.

For additional details, see Steven Frisbee's Facility review, below.

C. Special Product Quality Labeling Recommendations (NDA only)

The recommendations in Yong Wang's Labeling review, below, were conveyed to the OND PM for consideration as the labeling is finalized:

D. Final Risk Assessment (see Attachment)



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Miller

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Comments: ATL for NDA 211284

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BIOPHARMACEUTICS

NDA: 211284

Drug Product Name / Strength: Temixys (Lamivudine/Tenofovir Disoproxil Fumarate)
Tablets, 300 mg/300 mg

Route of Administration: Oral

Applicant Name: Celltrion, Inc.

Background:

Celltrion, Inc. is seeking approval for an immediate-release, film-coated, debossed, Fixed Dose Combination (FDC) Tablet containing 300 mg/300 mg of lamivudine/tenofovir disoproxil fumarate, respectively, to be administered orally once daily for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg *via* the 505(b)(2) regulatory pathway. This NDA (211284) is submitted under the President's Emergency Plan for Aids Relief (PEPFAR) program.

The submission is supported by a single center, single dose, open-label, randomized, two-treatment, two-period, cross-over study (CT-G02) to establish bio-equivalence (BE) between the bio-batch CBAU002F of the proposed Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg and the Listed Drugs, Epivir® Tablets, 300 mg (lamivudine) approved under the NDA 020564 and Viread® Tablets, 300 mg (tenofovir disoproxil fumarate) approved under the NDA 021356.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, and **3)** the need for bridging of the formulations, manufacturing sites, manufacturing process, and drug product image/coating/debossing throughout the product development.

Based on the review of the provided information/data, the conclusions of this Biopharmaceutics review are summarized as follows:

Proposed Dissolution Method: The dissolution method for the proposed drug product was developed using USP Apparatus 2 at a paddle speed of 50 rpm in 900 mL of 0.1 N HCl. The proposed dissolution method has limited ability (b) (4) in the drug product at early sampling time-points of up to (b) (4) minutes. However, the dissolution method does not have the ability to discriminate towards changes in the formulation and manufacturing process at the 20 minute time point. The dissolution method described below is acceptable as a quality control tool for dissolution testing of the 300 mg/300 mg strength lamivudine and tenofovir disoproxil fumarate tablets at batch release and for stability testing.

Parameters	Method
Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Media/Volume	0.1 N HCl /900 mL
Bath temperature	37.0±0.5°C

- **Proposed Dissolution Acceptance Criterion:** The dissolution acceptance criterion ‘Q= (b) (4) % in (b) (4) minutes’ originally proposed by the Applicant for the proposed 300 mg/300 mg FDC Tablets, is permissive. The dissolution data for three registration batches support a dissolution acceptance criterion of ‘Q= (b) (4) % in 20 minutes’ at batch release and for stability testing of the proposed drug product. In response to an Information Request comment, the Applicant agreed to the recommended dissolution acceptance criterion of ‘Q= (b) (4) % in 20 minutes’ for batch release and stability testing of Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg.

Originally Proposed Dissolution Acceptance Criterion	Q= (b) (4) % in (b) (4) minutes for 300 mg/300 mg strength Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets
FINAL Agreed Upon Dissolution Acceptance Criterion	Q=8 (b) (4) % in (b) (4) minutes for 300 mg/300 mg strength Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets

- **Bridging of the Formulations:** No bridging is necessary as there are no changes in the formulation, manufacturing process, manufacturing site, or drug product image/coating/debossing.
- **Biopharmaceutics Risk Assessment:** From a Biopharmaceutics perspective, though tenofovir disoproxil fumarate is hygroscopic, because the proposed drug product was manufactured using (b) (4) (b) (4) Furthermore, because lamivudine and tenofovir disoproxil fumarate are highly soluble drug substances (per BCS) and the proposed drug product exhibits an immediate-release dissolution profile, the risk of failing the dissolution test is low.
- **OVERALL REVIEW RECOMMENDATION:**
From the Biopharmaceutics perspective, NDA 211284 for Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg is recommended for **APPROVAL**.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Pamali Chatterjee, Ph.D., 08/15/2018

Secondary Biopharmaceutics Reviewer Name and Date:

Elsbeth Chikhale, Ph.D., 08/20/2018



**QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics**



BIOPHARMACEUTICS ASSESSMENT

➤ **LIST OF SUBMISSIONS REVIEWED:**

Submissions Reviewed	Reference ID
Original NDA Submission 211284	Dated 01/16/2018, SDN 1 (\\cdsesub1\evsprod\nda211284\0000\m2\23-qos\quality-overall-summary-dp-lmv-tdf-tablets.pdf)
Response to Information Request Comment #1	Dated 04/06/2018, SDN 5 \\cdsesub1\evsprod\nda211284\0004\m1\us\cover-letter-appendix-3.pdf
Response to Information Request Comment #2	Dated 06/27/2018, SDN 5 \\cdsesub1\evsprod\nda211284\0007\m1\us\cover-letter-appendix-3.pdf

➤ **DRUG PRODUCT:**

The proposed drug product will be available as oblong shaped, immediate-release, film-coated, debossed with 'C 0' on one side and plain on the other side, Fixed Dose Combination (FDC) tablets containing 300 mg/300 mg of lamivudine/tenofovir disoproxil fumarate, respectively. The recommended dose is one tablet to be taken orally once daily in combination with other antiretroviral agents for the treatment of HIV-1 in adults and pediatric patients weighing at least 35 kg.

The drug product is composed of lamivudine and tenofovir disoproxil fumarate as actives and (b) (4) croscarmellose sodium, (b) (4) (b) (4) and magnesium stearate as the excipients. (b) (4)

(b) (4)

➤ **MANUFACTURING SITES FOR THE PROPOSED DRUG PRODUCT:**

The Applicant identified (b) (4) Korea as the manufacturing and stability testing site for the drug product, including the site where dissolution testing of the final drug product is conducted.

Table 1. Qualitative and Quantitative Composition of
Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg

(b) (4)



➤ **BCS DESIGNATION**

An official BCS designation for the proposed drug product was not requested in the current submission. The active ingredients in the proposed drug product are lamivudine and tenofovir disoproxil fumarate. (b) (4)

[Redacted text]

According to the Applicant, tenofovir disoproxil fumarate, a di-ester prodrug is slightly hygroscopic, whereas lamivudine is not hygroscopic.

- **Solubility:**

The equilibrium solubility of lamivudine and tenofovir disoproxil fumarate drug substances was determined in buffer solutions across the physiological pH range 1.2-6.8 at 37°C as shown in **Table 2** (refer to: <\\cdsesub1\evsprod\nda211284\0000\m3\32-body-data\32p-drug-prod\lamivudine-and-tdf-tablets-300mg-cltpharm\32p2-pharm-dev\pharmaceutical-development.pdf>).

Table 2. Solubility Profile of Lamivudine and Tenofovir Disoproxil Fumarate in Buffer Solutions Across the Physiological pH Range 1.2-6.8 at 37 C

pH 4.5 ac
pH 6.8 pho

Reviewer’s Assessment of Drug Substance Solubility:

From **Table 2**, it can be concluded that lamivudine and tenofovir disoproxil fumarate exhibit a pH-dependent high solubility profile, with the highest solubility observed in 0.1 N HCl (pH=1.2). The highest dose for both lamivudine and tenofovir disoproxil fumarate in the drug product is 300 mg, which would be soluble in 250 mL across the physiological pH range 1.2-6.8. Accordingly, both lamivudine and tenofovir disoproxil fumarate can be classified as highly soluble drug substances.

- **Permeability:**

The Absorption, Distribution, Metabolism, and Excretion (ADME) data for the individual Listed Drugs (LD), Epivir® Tablets (Lamivudine) and Viread® Tablets (Tenofovir Disoproxil Fumarate), were referenced to support the ADME profile of lamivudine and tenofovir disoproxil fumarate in the proposed FDC product.

Briefly, lamivudine is rapidly absorbed and extensively distributed following a single oral administration of 150 mg and 300 mg Epivir® Tablets taken once daily for 7 days. The absolute bioavailability of lamivudine is approximately 86% for the 150 mg tablet and the oral solution. The rate of lamivudine absorption is slower following food intake, however there is no effect on the extent of absorption. The majority (~71%) of lamivudine is excreted unchanged in urine by active organic cationic transporters.

Tenofovir disoproxil fumarate exhibits approximately 25% bioavailability under fasted conditions following oral administration of a single 300 mg dose. The pharmacokinetics of tenofovir increases in a dose proportional manner following single and multiple dosing.

Reviewer’s Assessment of Absorption:

Based on the information provided by the Applicant, it can be concluded that lamivudine exhibits moderate gastro-intestinal permeability. However, tenofovir disoproxil fumarate exhibits low gastro-intestinal permeability.

Particle Size Distribution:

The Applicant included particle size distribution (PSD) as a control for lamivudine and tenofovir disoproxil fumarate drug substance (see **Table 3**). Though PSD control was included for both drug substances, particle size will not have an impact on the dissolution rate of the drug product as both drug substances exhibit high aqueous solubility across the physiological pH range 1.2-6.8.

Table 3. Particle Size Distribution Acceptance Criteria for Lamivudine and Tenofovir Disoproxil Fumarate Drug Substances

	Particle Size Distribution (PSD) in microns (µm)		
	D10	D50	D90
Lamivudine	(b) (4)		
Tenofovir Disoproxil Fumarate	(b) (4)		

➤ ***DISSOLUTION INFORMATION:***

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product and is utilized during the product development process, for the batches used in the pivotal clinical PK studies, and for batches on stability as a quality control tool. The dissolution method was also used to select the final drug product formulation and final manufacturing process.

➤ ***PROPOSED DISSOLUTION METHOD:***

The Applicant developed a single dissolution method for monitoring the release of lamivudine and tenofovir disoproxil from the proposed FDC drug product based on the dissolution methods listed in the FDA dissolution methods database for lamivudine and tenofovir disoproxil fumarate drug products.

The dissolution method and dissolution acceptance criterion proposed by the Applicant for the dissolution testing of the proposed FDC drug product are shown in **Table 4**.

Table 4. Proposed Dissolution Method and Dissolution Acceptance Criterion for Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg

Parameters	Method
Apparatus/Speed	USP Apparatus 2 (paddle)/ 50 rpm
Media/Volume	0.1 N HCl/900 mL
Bath temperature	37.0±0.5 C
Dissolution Acceptance Criterion for	Lamivudine and Tenofovir Disoproxil Fumarate ' Q= $\frac{(b)}{(4)}$ % in $\frac{(b)}{(4)}$ minutes '

➤ **Dissolution Medium:**

(b) (4)

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➤ **PROPOSED DISSOLUTION ACCEPTANCE CRITERIA:**

Recommended Dissolution Acceptance Criteria	
Temixys (lamivudine and tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg strength	Q = $\frac{(b)}{(4)}$ % in 20 minutes

The Applicant originally proposed 'Q = $\frac{(b)}{(4)}$ % in $\frac{(b)}{(4)}$ minutes' as the dissolution acceptance criteria for batch release and stability testing of Temixys (lamivudine/tenofovir disoproxil fumarate) Tablets, 300 mg/300 mg. To support the proposed dissolution acceptance criteria for the drug product, the Applicant provided dissolution data for bio-batch and two other registration batches at batch release and on stability for up to 9 months that will be reviewed below.

Reviewer's Assessment of the Proposed Dissolution Acceptance Criteria:

A review of the dissolution profile data for the 300/300 mg strength clinical batch CBAU002F used in the single center, single dose, open-label, randomized, two-treatment, two-period, cross-over study (CT-G02) and two other registration batches (shown in **Figure 4**) indicates that the dissolution data support the dissolution acceptance criteria of 'Q = $\frac{(b)}{(4)}$ % in 20 minutes' for both, lamivudine and tenofovir disoproxil.

Figure 4. Dissolution Profile Data for Lamivudine (LMV, **Panel A**) for the Bio-Batch CBAU002F and Two Registration Batches at Batch Release using the Proposed Dissolution Method

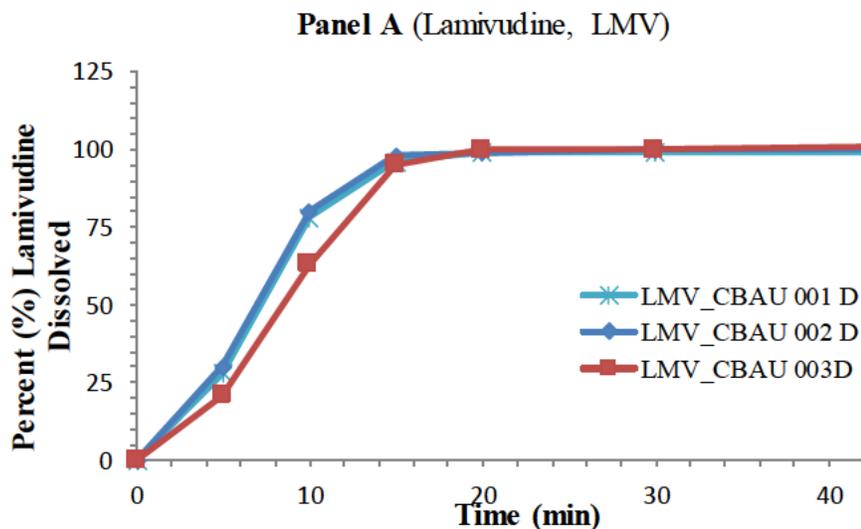
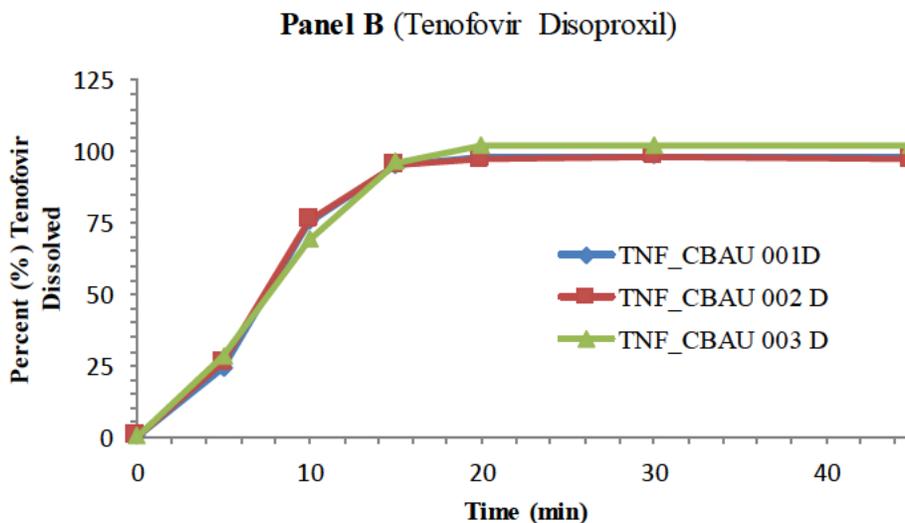


Figure 4. Dissolution Profile Data for Tenofovir Disoproxil (TNF, **Panel B**) for the Bio-Batch CBAU002F and Two Registration Batches at Batch Release using the Proposed Dissolution Method



Further, dissolution profile data for the batches on long-term stability at 25°C/60% RH for 9 months supports the dissolution acceptance criterion of $Q = \frac{(6)}{(4)}\%$ in 20 minutes for both, lamivudine and tenofovir disoproxil (see **Figure 5**).

Figure 5. Dissolution Profile Data for Lamivudine (LMV, **Panel A**) for the Bio-Batch CBAU002F and Two Registration Batches after Nine (9) months storage at Long-Term Stability (25° C/60% RH) using the Proposed Dissolution Method

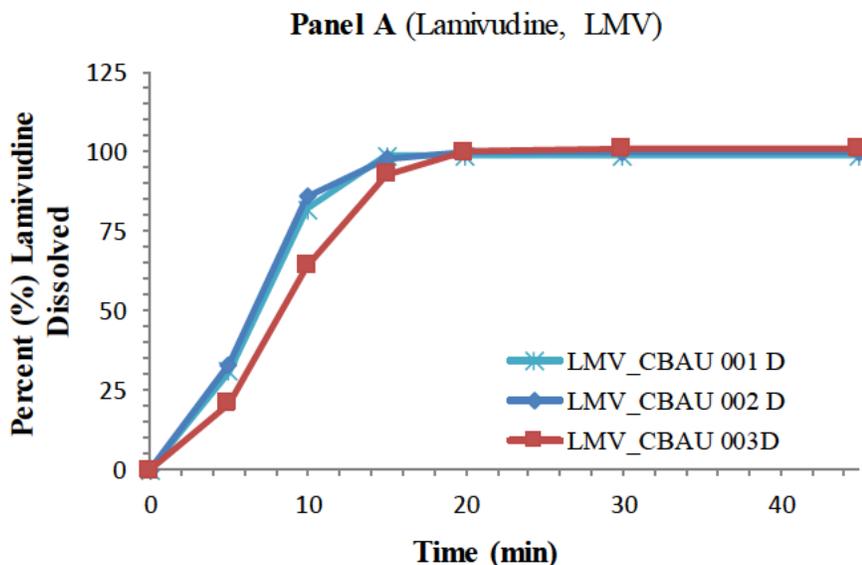
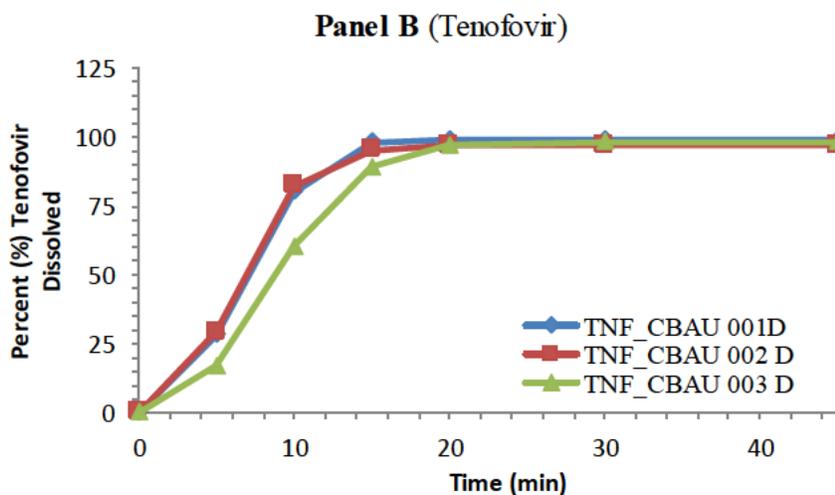


Figure 5. Dissolution Profile Data for Tenofovir Disoproxil (TNF, **Panel B**) for the Bio-Batch CBAU002F and Two Registration Batches after Nine (9) months storage at Long-Term Stability (25° C/60% RH) using the Proposed Dissolution Method



Based on the dissolution profile data provided in **Figure 4** and **Figure 5** (Panel A and B), 'Q= $\frac{(b)}{(4)}$ % in 20 minutes' is recommended for lamivudine and tenofovir disoproxil in the drug product. An Information Request comment was conveyed to the Applicant on 05/27/2018 to implement 'Q= $\frac{(b)}{(4)}$ % in 20 minutes' for lamivudine and tenofovir disoproxil. In response to the Information Request comment dated 06/27/2018, the Applicant agreed to the dissolution acceptance criteria of 'Q= $\frac{(b)}{(4)}$ % in 20 minutes' for lamivudine and tenofovir disoproxil.

Reviewer's Assessment of the Proposed Dissolution Method:

Based on the totality of the dissolution data, from a Biopharmaceutics perspective, the proposed dissolution method is adequate for batch release and stability testing of the produced FDC drug product. The analytical method (HPLC/UV) associated with the proposed dissolution method will be evaluated by the CMC Reviewer.

➤ *Bridging of the Formulations:*

No bridging of formulations, image/coating/debossing, and the manufacturing site or process is necessary as there are no changes in the formulation, tablet image, manufacturing site or manufacturing process between the Bio-Batch and the proposed commercial drug product.

➤ *BIOPHARMACEUTICS RISK ASSESSMENT:*

From a Biopharmaceutics perspective, though tenofovir disoproxil fumarate is hygroscopic, because the proposed drug product was manufactured using (b) (4)
(b) (4)

Furthermore, because lamivudine and tenofovir disoproxil fumarate are highly soluble drug substances (per BCS) and the proposed drug product exhibits an immediate-release dissolution profile, the risk of failing the dissolution test is low.

➤ *POST-APPROVAL COMMITMENTS: None***➤ *LIST OF DEFICIENCIES: None*****➤ *OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 211284 for Lamivudine and Tenofovir Disoproxil Fumarate Film-Coated Tablets, 300 mg/300 mg is recommended for **APPROVAL**.

➤ *SIGNATURES****Primary Biopharmaceutics Reviewer Name and Date:***

Parnali Chatterjee, Ph.D., 08/15/2018

Secondary Reviewer Name and Date:

Elsbeth Chikhale, Ph.D., 08/20/2018

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Chatterjee

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Elsbeth
Chikhale

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

Final Risk Table for Lamivudine and Tenofovir DF Tablets (NDA 211284)

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		Acc	
Physical stability (solid state)		L	Drug substance manufacturing processes produce consistent solid state forms. (b) (4)	Acc	
Content uniformity	(b) (4)	M	(b) (4)	Acc	
Microbial limits		L		Acc	
Dissolution – BCS Class I & III	Both DS exhibit high water solubility and low gastrointestinal permeability.	L	Dissolution acceptance criterion (b) (4) Q = (b) (4)% in 20 minutes for both actives	Acc	Dissolution method exhibits limited discriminatory power at the 20 minute time point because both drug substances are highly soluble and the drug product is an immediate-release drug product
Patient Use Considerations	No instructions for dispersion or splitting	L		Acc	



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/s/

KYONG M HYON
11/21/2018

LABELING

IQA Review Guide Reference

NDA 211284

I. Package Insert

1. Highlights of Prescribing Information

These highlights do not include all the information needed to use TEMIXYS safely and effectively. See full prescribing information for TEMIXYS.

TEMIXYS (lamivudine and tenofovir disoproxil fumarate) tablets, for oral use
Initial U.S. Approval: YYYY

-----DOSAGE FORMS AND STRENGTHS-----

- Tablet: 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	TEMIXYS lamivudine and tenofovir disoproxil fumarate)
Dosage form, route of administration	tablets, for oral use
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablet: 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate

2. Section 2 Dosage and Administration

2.1 Recommended Dose in Adults and Pediatric Patients Weighing at least 35 kg

The recommended dose of TEMIXYS (containing 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) is one tablet taken orally once daily with or without food.

2.2 Patients with Renal Impairment

Because TEMIXYS is a fixed-dose combination, (b) (4) for patients (b) (4) with (b) (4) renal (b) (4) (b) (4) creatinine clearance (b) (4) 50 mL/min).

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)	one tablet taken orally once daily with or without food.

3. Section 3 Dosage Forms and Strengths

TEMIXYS contains 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. (b) (4) white, oblong shape, film-coated tablets debossed with “C 0” on one side and plain on the other side.

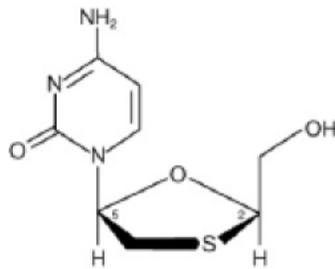
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablet
Strengths: in metric system	300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate
Active moiety expression of strength with equivalence statement (if applicable)	300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. Acceptable per labeling review tool (02/2017)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white, oblong shape, film-coated tablets debossed with “C 0” on one side and plain on the other side

4. Section 11 Description

TEMIXYS is for oral administration. Each film coated tablet contains 300 mg of Lamivudine and 300 mg of Tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil). In addition, each tablet contains the following inactive ingredients: (b) (4) croscarmellose sodium, magnesium stearate, cellactose 80 (lactose monohydrate and powdered cellulose), colloidal silicon dioxide, and (b) (4) white which contains hypromellose, titanium dioxide and polyethylene glycol.

Lamivudine

Lamivudine, a synthetic nucleoside analogue with activity against HIV-1 and HBV. The chemical name of lamivudine is (b) (4). 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 C₈H₁₁N₃O₃S and a molecular weight of 229.26 g per mol. It has the following structural formula:

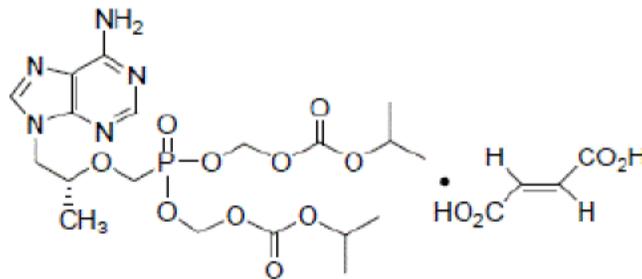


Lamivudine is a white to off-white (b) (4) water.

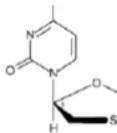
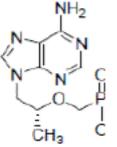
Tenofovir disoproxil fumarate

(b) (4)

The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2-[[bis[[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]methoxy]propyl]adenine fumarate (1:1). It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52. It has the following structural formula:



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	TEMIXYS Lamivudine and Tenofovir disoproxil fumarate
Dosage form and route of administration	TEMIXYS is for oral administration.
Active moiety expression of strength with equivalence statement (if applicable)	Each film coated tablet contains 300 mg of Lamivudine and 300 mg of Tenofovir disoproxil fumarate (equivalent to 245 mg of tenofovir disoproxil).
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>)	In addition, each tablet contains the following inactive ingredients: cellactose 80 (lactose monohydrate and powdered cellulose), colloidal silicon dioxide, croscarmellose sodium, (b) (4) magnesium stearate, and (b) (4) a film coating which contains hypromellose, polyethylene glycol, and titanium dioxide. <i>Please list all inactive ingredients in alphabetical order.</i>
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	(b) (4)

<p>Chemical name, structural formula, molecular weight</p>	<p>The chemical name of lamivudine is (b) (4)</p> <p>Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.26 g per mol.</p>  <p>The chemical name of tenofovir disoproxil fumarate is 9-[(R)-2-[[[bis[[[isopropoxycarbonyl]oxy]methoxy]phosphiny]methoxy]propyl]adenine fumarate (1:1).</p>  <p>It has a molecular formula of $C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4$ and a molecular weight of 635.52.</p>
<p>If radioactive, statement of important nuclear characteristics.</p>	<p>NA</p>
<p>Other important chemical or physical properties (such as pKa or pH)</p>	<p>TFA has a partition coefficient (log p) of (b) (4).</p>

5. Section 16 How Supplied/Storage and Handling

TEMIXYS is white, oblong shape, film-coated tablets debossed with “C 0” on one side and plain on the other side.

30 tablets in HDPE bottle with desiccant, induction seal, and child-resistant closure NDC 32228-004-01

(b) (4)

(b) (4) Store below 30°C

(86 °F).

Keep bottles tightly closed to protect from moisture.

Dispense and store only in original container.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	TEMIXYS (300mg/300mg)
Available units (e.g., bottles of 100 tablets)	30 tablets in HDPE bottle
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<p>TEMIXYS is white, oblong shape, film-coated tablets debossed with “C 0” on one side and plain on the other side.</p> <p>30 tablets in HDPE bottle NDC 32228-004-01</p> <p>(only the bottle of 30 tablets will be distributed in U.S)</p>
Special handling (e.g., protect from light)	<p>Keep bottles tightly closed to protect from moisture.</p> <p>Dispense and store only in original container.</p>
Storage conditions	<p>Store (b) (4)</p> <p>Keep bottles tightly closed to protect from moisture.</p> <p>The storage conditions should be replaced with the following:</p> <p>Store below 30°C (86 °F) Keep bottles tightly closed to protect from moisture.</p> <p>Dispense and store only in original bottle.</p>
Manufacturer/distributor name (21 CFR 201.1(h)(5))	<p>Manufactured by: CELLTRION PHARM, INC. 82, 2sandan-ro, Ochang-eup, Cheongwon-gu, Cheongju-si, Chungcheongbuk-do, 28117, Republic of Korea</p> <p>Distributed by: CELLTRION, INC. 23 Academy-ro, Yeonsu-gu, Incheon, 22014, Republic of Korea</p>

Patient Information:

How should I store TEMIXYS?

- Store TEMIXYS tablets (b) (4) below 30°C (86 °F).
- Keep TEMIXYS in the original bottle.
- Keep bottles of TEMIXYS tightly closed.
- Do not use TEMIXYS if the seal over the bottle opening is broken or missing.
- (b) (4)

Keep TEMIXYS and all medicines out of the reach of children.

General information about the safe and effective use of TEMIXYS.

Reviewer's Assessment of Package Insert: {Adequate/Inadequate}

For package insert review, all the proposed changes (in blue) have been communicated to the applicant as indicated in Dr. S. Miller's email dated August 3, 2018.

{Assess if the Prescribing Information complies with all regulatory requirements from a CMC perspective}

➤ *Any deficiencies should be listed at the end in the "List of Deficiencies"*

II. Labels:**1. Container and Carton Labels**

(b) (4)

{Copy/paste or refer to a representative example of a proposed container}

2. Carton Label

N/A

{Copy/paste or refer to a representative example of a proposed carton labels}

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)))	<p>TEMIXYS Lamivudine 300 mg / Tenofovir disoproxil fumarate 300 mg tablets</p> <p>For font size and formats of the strength and established name, refer to DMEPA review by Dr. Valerie Wilson.</p>	
Dosage strength	Lamivudine 300 mg / Tenofovir disoproxil fumarate 300 mg tablets	
Net contents	30 tablets 60 tablets (not for US market) 100 tablets (not for US market)	
"Rx only" displayed prominently on the main panel	"Rx only"	
NDC number (21 CFR 207.35(b)(3)(i))	30 tablets in HDPE bottle NDC 32228-004-01	
Lot number and expiration date (21 CFR 201.17)	<p>Spaces for lot number and expiration are available</p> <p>For format of expiry date, refer to DMEPA review by Dr. Kyong Hyon regarding suggestions about format of the expiration date.</p>	

Storage conditions	<p>(b) (4)</p> <p>Dispense only in original (b) (4).</p> <p>See package insert for dosage and administration.</p> <p>The above storage conditions should be revised as the following:</p> <p><i>Store below 30°C (86 °F). This package is child-resistant. Keep bottles tightly closed to protect from moisture. Dispense and store only in original bottle. See package insert for dosage and administration.</i></p>	
Bar code (21CFR 201.25)	Available	
Name of manufacturer/distributor	<p>Distributed by: Celltrion, Inc. Incheon, S. Korea 22014</p> <p>Manufactured by: Celltrion, Inc. Cheongju, S. Korea 28117,</p>	
And others, if space is available		

Reviewer’s Assessment of Labels: Adequate

For container label review, all the proposed changes (in blue) have been communicated to the applicant as indicated in DMEPA’s review by Dr. V. Wilson dated August 2, 2018 and Dr. S. Miller’s email dated August 3, 2018.

{Assess if the labels comply with all regulatory requirements from a CMC perspective}

➤ *Any deficiencies should be listed at the end in the “List of Deficiencies”*

List of Deficiencies: None

All proposed changes were communicated to the applicant as described in Dr. S. Miller’s email dated August 3, 2018.

Overall Assessment and Recommendation:

Primary Labeling Reviewer Name and Date:

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



Yong
Wang

Digitally signed by Yong Wang
Date: 8/26/2018 04:55:36PM
GUID: 508da7210002a01861739fd87b35adb9



Stephen
Miller

Digitally signed by Stephen Miller
Date: 8/27/2018 09:17:36AM
GUID: 508da7210002a000609476bbeecd040f0
Comments: For B.Shanmugam