

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210649Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210649
Review #3 (Resub-9)

Drug Name/Dosage Form	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Strength	400 mg/300 mg/300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Macleods
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resub-9	Sept 17, 2018	Facilities and DS
Amendment	Oct 16, 2018	Quality
Amendment	Oct 22, 2018	Quality
Amendment	Nov 27, 2018	Quality
Amendment	Jan 4, 2019	Quality
Amendment	Jan 22, 2019	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Haripada Sarker
Drug Product	Yong Wang	Balajee Shanmugam
Process & Microbiology	Christine Falabella	Arwa El Hagrasy
Facility	Frank Wackes	Ying Zhang
Biopharmaceutics	Zhuojun (Joan) Zhao	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)	(b) (4)	Adequate	Apr 21, 2017	Rev under DMF in Pano
	Type II		(b) (4)	Adequate	July 19, 2018	Rev under DMF in Pano
	Type II		(b) (4)	Adequate	Nov 29, 2018	Rev under DMF in Pano
Various	Type III	See DP review				
	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/ucm119231.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

This NDA is recommended for **Approval** from the product quality perspective.

II. Summary of Quality Assessments

A. Product Overview

This is a resubmission after CR for this three-drug combination tablet containing the lower dose of efavirenz (400mg). This NDA received a Complete Response on Sept 12, 2018 due to inspectional concerns related to the tablet manufacturing facility (Macleods-Baddi; FEI 3007517881). In this resubmission, the Baddi facility was withdrawn as a proposed commercial manufacturing site and was replaced by an alternate facility, Macleods Pharmaceuticals Limited – Daman (FEI 3006363714), which successfully executed and submitted a new exhibit batch and stability data.

Proposed Indication(s) including Intended Patient Population	Indicated (b) (4) for the treatment of HIV-1 infection in adults and (b) (4) weighing at least (b) (4) kg.
Duration of Treatment	Chronic, until resistance develops.
Maximum Daily Dose	One tablet daily on an empty stomach,
Alternative Methods of Administration	None

B. Quality Assessment Overview

Facilities:

An inspection of the Daman tablet-manufacturing facility was conducted Jan 21-25, 2019. Based on the initial field recommendation from that inspection, and an evaluation of the previous inspection (May 2017), this facility is considered to be acceptable for the intended commercial operations of NDA 210649.

All other facilities are acceptable at this time. An overall Manufacturing Facility Status recommendation of Approve was entered in to Panorama on Feb 2, 2019. For additional information, see Frank Wackes' facility review attached below, the facility review in the OPQ Rev-1 dated Mar 13, 2018, and the executive summary section of OPQ Rev-2 (Aug 27, 2018).

Drug Substance:

Amendments to the three drug substance DMFs were evaluated, and all three are adequate at this time. See Table A on the previous page for the dates of the most recent

DMF reviews. For additional information, see Haripada Sarker's drug substance review, below, and the drug substance sections of OPQ Rev-1 (Mar 13, 2018) and OPQ Rev-2 (Aug 27, 2018).

Drug Product:

New information reviewed under Resub-7:

In this resubmission there are no changes to the drug product formulation or to the container-closure systems. The proposed drug product specifications for release and regulatory (shelf-life) manufactured at the proposed Daman site remain unchanged compared to the previous review cycle and remain acceptable. An adequate risk assessment for elemental impurities was included in this resubmission. The analytical method for assay has been modified for sample preparation procedure. Therefore, the assay method has been revalidated. All validation results met the acceptance criteria. The assay method is adequate for its intended use. In addition, method transfer reports for assay, related substances, dissolution release rates, and (b) (4) demonstrated high agreement between Daman (receiving site) and Himachal Pradesh (originating site). The release data for the Daman batch (EED7801) are comparable to those from the Baddi batches (BEB3601, BEB3602 and BEB3603). The only attribute which changes on stability is the degradant, (b) (4). While somewhat (b) (4) was seen under accelerated conditions for the bottles of 90 and 180, at the long-term condition of 30°C/75%RH, the stability of all of the Daman packaging configurations were comparable to that of the Baddi products. These release and comparative 3-month stability results, in conjunction with the 6-month data on the Baddi batches, support the proposed 12-month expiration dating period.

Background Information from previous DP reviews:

Pink colored, capsule shaped, biconvex film coated tablets debossed with "F 31" on one side and plain on other side. The tablet weighs 1.5 grams. After tightening limit for (b) (4) from NMT (b) (4) % to NMT (b) (4) %, the drug product specification is acceptable. The revised specification, including the revisions to the dissolution procedure, are shown in the "proposed-specifications" document submitted on Feb 21, 2018. Macleods provided an acceptable risk assessment (in 3.2.P.2) showing that all the probable elemental impurities in the drug product are well within the permitted daily exposures under ICH Q3D and USP <232>.

Stability data out to 9 months (Batch BEB3601) and 6 months (remaining 3 batches) were provided, with results supporting the proposed 12-month expiration dating period. The product is proposed to be packaged in three configurations:

- Bottle of 30 tablets with desiccant, induction seal and child-resistant cap
- Bottle of 90 tablets with desiccant, induction seal and child-resistant cap
- Bottle of 180 tablets with desiccant, induction seal and non-child-resistant cap

An in-use study in which the bottle of 180 tablets was opened and sampled four times over the 180-day study duration supported the quality of the tablet as used by patients.

For additional information, see Yong Wang's drug product review, below, and the drug product information in OPQ Rev-1 (Mar 13, 2018) and OPQ Rev-2 (Aug 27, 2018).

Process:**New information reviewed under Resub-7:**

At the new drug product manufacturing site, the applicant has manufactured 1 registration batch (EED7801) with batch size of (b) (4) tablets and submitted executed master batch records and master packaging records for that batch. The applicant has proposed different intended commercial batch sizes for the largest ((b) (4) tablets) and smallest ((b) (4) tablets) batches. The previously proposed commercial batch sizes from Seq. 000 were (b) (4) tablets for the smallest commercial batch and (b) (4) tablets for the largest commercial batches (10x scale-up). In the original submission, the applicant had manufactured 4 registration batches ((b) (4) tablets/batch) at the former site (Baddi). The single registration batch manufactured at the new site (Daman) were compared with those previously manufactured registration batches. (b) (4)

(b) (4)

(b) (4) The in-process, release, and stability test results were similar among the 4 registration batches from the Baddi site and the 1 registration batch from the new Daman site were similar when compared side-by-side, which would suggest that the applicant has sufficient knowledge to manufacture the drug product at the Daman site.

Background Information from previous DP reviews:

The proposed drug product is a (b) (4) tablet composed of (b) (4) Efavirenz (400 mg) (b) (4) Lamivudine (300 mg) and Tenofovir Disoproxil Fumarate 300 mg (b) (4)

(b) (4)

(b) (4)

Upon request, the applicant revised the in-process controls

(b) (4)

(b) (4)

(b) (4) The commercial process will use the BEB7701 formulation, at two scales: (b) (4) and (b) (4) tablets. Based on release results, and dissolution comparisons (see Biopharmaceutics section, below), the intended commercial formulation and process is acceptable.

For the release specifications of the finished tablets, the applicant proposed to use

(b) (4)

(b) (4) After further justification

including a

(b) (4)

(b) (4) the attributes of the drug product specification related to microbial controls were judged to be acceptable. For additional information, see Christine Falabella's process/microbiology review, below, and the process/microbiology information in OPQ Rev-1 (Mar 13, 2018) and OPQ Rev-2 (Aug 27, 2018).

Biopharmaceutics:

This Biopharmaceutics review assesses the dissolution data generated to support the addition of Macleods-Daman as the drug product manufacturing site. Tablets manufactured at the original (Baddi) and the new (Daman) manufacturing sites showed similar dissolution profiles. Therefore, the Applicant's request for the new drug product manufacturing site (Daman) is acceptable from the Biopharmaceutics perspective.

Based on the provided dissolution data, the following revised dissolution methods and acceptance criterion are acceptable and were agreed upon in Rev-1 (Mar 13, 2018):

- Efavirenz: $Q = \frac{(b)(4)}{(4)}\%$ in 20 min using 1000 mL 2% SLS in water; Apparatus II (paddle) at 100 rpm
- Lamivudine & Tenofovir DF: $Q = \frac{(b)(4)}{(4)}\%$ in 20 min using 900 mL 0.1N HCl; Apparatus II (paddle) at 75 rpm

The registration batches (including the Biobatch BEB3601) differ from the proposed commercial batches in terms of the description of the tablets (b) (4)

(b) (4) The Applicant provided adequate comparative dissolution data supporting the bridge between the Biobatch and the commercial image/formulation. For additional information, see Zhuojun (Joan) Zhao's biopharmaceutics review, below, and the biopharmaceutics information in OPQ Rev-1 (Mar 13, 2018) and OPQ Rev-2 (Aug 27, 2018).

C. Special Product Quality Labeling Recommendations (NDA only)

The recommendations in Yong Wang's Labeling Review, attached below, should be considered during labeling negotiations.

D. Final Risk Assessment (see Attachment)



Stephen
Miller

Digitally signed by Stephen Miller

Date: 2/22/2019 03:47:44PM

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Comments: ATL for NDA 210649 Resub-9

LABELING[IQA Review Guide Reference](#)**NDA 210649****I. Package Insert****1. Highlights of Prescribing Information**

These highlights do not include all the information needed to use efavirenz, lamivudine and tenofovir disoproxil fumarate safely and effectively. See full prescribing information for efavirenz, lamivudine and tenofovir disoproxil fumarate tablets.

Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg

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

Tablets: 400 mg efavirenz, 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	Proprietary name: N/A efavirenz, lamivudine and tenofovir disoproxil fumarate
Dosage form, route of administration	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg. The applicant should use the following: <i>Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg for oral use</i>
Controlled drug substance symbol (if applicable)	Not Applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 400 mg efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate.

2. Section 2 Dosage and Administration

2.1 Recommended Dose in Adults and (b) (4) (weighing at least (b) (4) kg)

The recommended dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate (containing 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) is one tablet per day taken orally on an empty stomach, preferably at bedtime.

2.2 (b) (4) Renal Impairment

Because Efavirenz, Lamivudine and Tenofovir disoproxil fumarate is a fixed-dose combination tablet, it is not recommended for patients with impaired renal function (creatinine clearance less than 50 mL/min) or patients with end-stage renal disease (ESRD) requiring hemodialysis.

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)	The recommended dose of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate (containing 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) is one tablet per day taken orally on an empty stomach, preferably at bedtime.

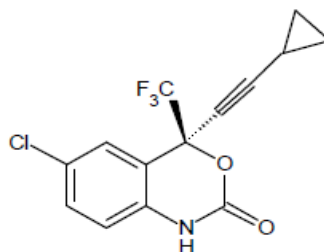
3. Section 3 Dosage Forms and Strengths

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate film-coated Tablets are pink colored, capsule shaped, biconvex, film coated tablets debossed with "F 31" on one side and plain on other side containing 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate. (b) (4)

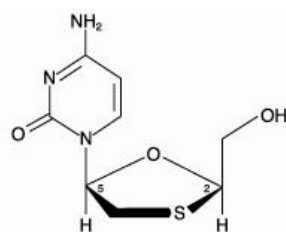
Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate film-coated Tablets
Strengths: in metric system	400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate
Active moiety expression of strength with equivalence statement (if applicable)	300 mg of tenofovir disoproxil fumarate (b) (4) (equivalence statement not needed in this section per CDER Labeling Review Tool) The following is recommended to the applicant: <i>Efavirenz, Lamivudine and Tenofovir disoproxil fumarate film-coated Tablets are pink colored, capsule shaped, biconvex, film coated tablets debossed with “F 31” on one side and plain on other side containing 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate.</i>
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate film-coated Tablets are pink colored, capsule shaped, biconvex, film coated tablets debossed with “F 31” on one side and plain on other side

4. Section 11 Description

Efavirenz: Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Efavirenz is chemically described as (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one. Its empirical formula is C₁₄H₉ClF₃NO₂ and its structural formula is:

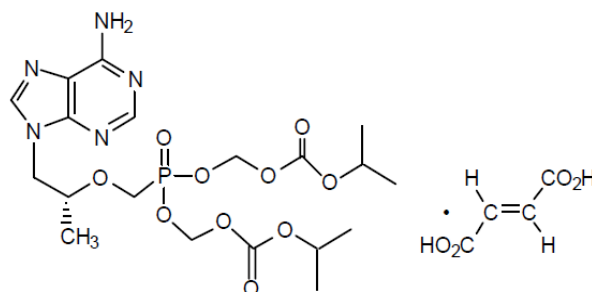


Lamivudine: The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)-enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)-2', 3' -dideoxy, 3' thiacytidine. It has a molecular formula of C₈H₁₁N₃O₃S and a molecular weight of 229.3 g per mol. It has the following structural formula:



Tenofovir: Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. In vivo tenofovir DF is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.

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:



Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25 C. It has an octanol/phosphate buffer (pH 6.5) partition coefficient (log p) of 1.25 at 25 C.

Each tablet contains 400 mg of Efavirenz, 300 mg Lamivudine and 300 mg of Tenofovir Disoproxil Fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: lactose monohydrate, croscarmellose sodium, poloxamer, hydroxypropyl cellulose, sodium lauryl sulphate, pregelatinised starch, magnesium stearate and microcrystalline cellulose. The tablets are coated with hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, ferric oxide red and triacetin. In this insert, all dosages are expressed in terms of Tenofovir Disoproxil Fumarate except where otherwise noted.

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	Proprietary name is not available.
Dosage form and route of administration	Tablet
Active moiety expression of strength with equivalence statement (if applicable)	Each tablet contains 400 mg of Efavirenz, 300 mg Lamivudine and 300 mg of Tenofovir Disoproxil Fumarate, which is 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>)	, and the following inactive ingredients: lactose monohydrate, croscarmellose sodium, poloxamer, hydroxypropyl cellulose, sodium lauryl sulphate, pregelatinised starch, magnesium stearate and microcrystalline cellulose. The tablets are coated with hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, ferric oxide red and triacetin. To list all excipients in in alphabetical order, the following is recommended: <i>....., and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, poloxamer, and sodium lauryl sulphate. The tablets are coated with ferric oxide red, hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin.</i>
Statement of being sterile (if applicable)	Not applicable

Pharmacological/ therapeutic class	Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine In vivo tenofovir DF is converted to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase.
Chemical name, structural formula, molecular weight	Available
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	

5. Section 16 How Supplied/Storage and Handling

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets 400mg/300mg/300mg are Pink colored, capsule shaped, biconvex, film coated tablets debossed with "F 31" on one side and plain on other side.

Bottle of 30 tablets with silica gel desiccant and induction seal - NDC 33342-362-07

Bottle of 90 tablets with silica gel desiccant and induction seal - NDC 33342-362-10

Bottle of 180 tablets with silica gel desiccant and induction seal - NDC 33342-362-57

Store (b) (4) 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	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate tablets 400mg/300mg/300mg
Available units (e.g., bottles of 100 tablets)	Bottle of 30 tablets with desiccant, induction seal and child-resistant cap Bottle of 90 tablets with desiccant, induction seal and child-resistant cap Bottle of 180 tablets
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink colored, capsule shaped, biconvex, film coated tablets debossed with “F 31” on one side and plain on other side
Special handling (e.g., protect from light)	Not applicable The following should be included in this section: <i>Store in the original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant.</i>
Storage conditions	Store (b) (4) below 30°C (86°F) The following is recommended to applicant: <i>Store below 30°C (86°F)</i>
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Macleods Pharma USA, Inc. Plainsboro, NJ 08536 Manufactured by: Macleods Pharmaceuticals Ltd. (b) (4) INDIA

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

The package is considered adequate upon resolving the following issue:

1. In the section of Highlights of Prescribing Information, please replace “Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg” with “Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg, for oral use”

2. In section 3 Dosage Forms and Strengths, the following description is recommended:

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate film-coated Tablets are pink colored, capsule shaped, biconvex, film coated tablets debossed with “F 31” on one side and plain on other side containing 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate.

3. To list all excipients in in alphabetical order, the following is recommended in section 11 Description

Each tablet contains 400 mg of Efavirenz, 300 mg Lamivudine and 300 mg of Tenofovir Disoproxil Fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, poloxamer, and sodium lauryl sulphate. The tablets are coated with ferric oxide red, hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin.

4. In Section 16 HOW SUPPLIED/STORAGE AND HANDLING, please include additional special handling requirement and modify the language for storage condition. Additionally, include the information of child-resistant cap for container closure systems of 30’s and 90’s packs with the following.

Store in the original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant.

Replace (b) (4) with “Store below 30°C (86°F)”.

Bottle of 30 tablets with silica gel desiccant, induction seal, and child-resistant cap - NDC 33342-362-07

Bottle of 90 tablets with silica gel desiccant, induction seal, and child-resistant cap - NDC 33342-362-10

{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

NA

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))	Proprietary name: N/A	Proprietary name: N/A
Dosage strength	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 400 mg/300 mg/300 mg	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 400 mg/300 mg/300 mg
Net contents	30 Tablets 90 Tablets 180 Tablets	30 Tablets 90 Tablets 180 Tablets
“Rx only” displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	NDC 33342-362-07 (30 Tablets) NDC 33342-362-10 (90 Tablets) NDC 33342-362-57 (180 Tablets)	NDC 33342-362-07 (30 Tablets) NDC 33342-362-10 (90 Tablets) NDC 33342-362-57 (180 Tablets)
Lot number and expiration date (21 CFR 201.17)	Available	Available

Storage conditions	Store below 30°C (86°F) For bottles of 30 and 90 tablets, include the following additional storage requirements. <i>This bottle is child-resistant. Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.</i> For a bottle of 180 tablets, include the following additional storage requirements. <i>Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.</i>	Store below 30°C (86°F) For bottles of 30 and 90 tablets, include the following additional storage requirements. <i>This bottle is child-resistant. Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.</i> For a bottle of 180 tablets, include the following additional storage requirements. <i>Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.</i>
Bar code (21CFR 201.25)	Available	Available
Name of manufacturer/distributor	Manufactured for: Macleods Pharma USA, Inc. Plainsboro, NJ 08536 Manufactured by: Macleods Pharmaceuticals Ltd. (b) (4)	Manufactured for: Macleods Pharma USA, Inc. Plainsboro, NJ 08536 Manufactured by: Macleods Pharmaceuticals Ltd (b) (4)
And others, if space is available	Each film-coated tablet contains: Efavirenz, USP 400 mg Lamivudine, USP 300 mg Tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil	Each film-coated tablet contains: Efavirenz, USP 400 mg Lamivudine, USP 300 mg Tenofovir disoproxil fumarate 300 mg equivalent to 245 mg of tenofovir disoproxil

Reviewer's Assessment of Labels: Adequate

Since (b) (4), the additional handling requirements should be included in the container labels.

In container labels for bottles containing 30 and 90 tablets, include the following additional storage requirements.

This bottle is child-resistant. Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.

In container label for bottles containing 180 tablets, include the following additional storage requirements.

Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.

{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:

The package is considered adequate upon resolving the following issue:

1. In the section of Highlights of Prescribing Information, please replace "Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg" with "Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg, for oral use"
2. In section 3 Dosage Forms and Strengths, the following description is recommended:

Efavirenz, Lamivudine and Tenofovir disoproxil fumarate film-coated Tablets are pink colored, capsule shaped, biconvex, film coated tablets debossed with "F 31" on one side and plain on other side containing 400 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate.
3. To list all excipients in in alphabetical order, the following is recommended in section 11 Description

Each tablet contains 400 mg of Efavirenz, 300 mg Lamivudine and 300 mg of Tenofovir Disoproxil Fumarate, which is equivalent to 245 mg of tenofovir disoproxil, and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, poloxamer, and sodium lauryl sulphate. The tablets are coated with ferric oxide red, hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin.

- 4 In Section 16 HOW SUPPLIED/STORAGE AND HANDLING, please include additional special handling requirement and modify the language for storage condition. Additionally, include the information of child-resistant cap for container closure systems of 30's and 90's packs with the following.

Store in the original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant.

Replace (b) (4) with "Store below 30°C (86°F)".

Bottle of 30 tablets with silica gel desiccant, induction seal, and child-resistant cap - NDC 33342-362-07

Bottle of 90 tablets with silica gel desiccant, induction seal, and child-resistant cap - NDC 33342-362-10

- 5 In container labels for bottles containing 30 or 90 tablets, include the following additional storage requirements.

This bottle is child-resistant. Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.

- 6 In container label for bottles containing 180 tablets, include the following additional storage requirements.

Store in the original bottle, protect it from moisture, and keep tightly closed. Do not remove desiccant. (b) (4) keep out of the reach of children.

Overall Assessment and Recommendation:

From a CMC perspective, the proposed labeling is considered adequate upon resolving the above deficiencies.

Primary Labeling Reviewer Name and Date:

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



Yong
Wang

Digitally signed by Yong Wang
Date: 2/15/2019 11:32:11AM
GUID: 508da7210002a01861739fd87b35adb9



Stephen
Miller

Digitally signed by Stephen Miller
Date: 2/15/2019 01:34:48PM
GUID: 508da7210002a000609476bbeed040f0

BIOPHARMACEUTICS

Product Background:

NDA: 210649-ORIG-1-RESUB-9 (505(b)(2)).

Drug Product Name / Strength: Efavirenz, Lamivudine and Tenofovir disoproxil fumarate IR Tablets, 400mg/300mg/300mg

Route of Administration: Oral

Applicant Name: Macleods Pharmaceuticals Limited

Review Summary:

The Applicant's originally proposed dissolution method and acceptance criteria were previously reviewed and found acceptable¹. The NDA was recommended for a COMPLETE RESPONSE (CR) due to unresolved inspectional findings for the tablet manufacturing facility (Macleods-Baddi)². This Biopharmaceutics review is an evaluation of the Applicant's resubmission in response to the CR letter dated September 12, 2018.

In this resubmission dated September 17, 2018 (0008), the Applicant proposes to add a new drug product manufacturing site (Macleods-Daman). The original tablet manufacturing site (Baddi) was withdrawn in an amendment dated October 22, 2018 (0010). This Biopharmaceutics review assesses the dissolution data generated to support the addition of Macleods-Daman as the drug product manufacturing site.

The Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets, 400mg/300mg/300mg manufactured at the original (Baddi) and the new (Daman) manufacturing sites showed similar dissolution profiles. Therefore, the Applicant's request for the new drug product manufacturing site (Daman) is acceptable for the proposed Efavirenz, Lamivudine and Tenofovir disoproxil fumarate IR Tablets, 400mg/300mg/300mg.

From the Biopharmaceutics perspective, NDA 210649 for Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets, 400mg/300mg/300mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name: Zhuojun Joan Zhao, Ph.D.

Secondary Reviewer Name: Elsbeth Chikhale, Ph.D.

¹ Panorama (NDA-210649-ORIG-1-REO-2); NDA 210649 007-IQA-BIOPHARMACEUTICS.docx (2/23/2018)

² Panorama (NDA-210649-ORIG-1-REO-2); NDA 210649 Exec Summ with Cover Pages.docx (3/13/2018)

Manufacturing Site

The Applicant proposes to add a new drug product manufacturing site, as shown below:

Approved Drug Product Manufacturing Site in Original NDA	Proposed Additional Drug Product Manufacturing Site
Macleods Pharmaceuticals Limited, Village Theda, Post Office Lodhimajra, Tehsil Baddi, District Solan, Baddi, Himachal Pradesh – 174101, India. Facility Establishment Identifier: 3007517881 DUNS 676369519	Macleods Pharmaceuticals Limited, Plot No. 25 – 27, Survey No. 366, Premier Industrial Estate, Kachigam, Daman – 396210, India Facility Establishment Identifier: 3006363714 DUNS 918608365

Based on the Process Reviewer Dr. Falabella, the manufacturing process and manufacturing equipment at the Daman site are very similar to those at the original Baddi site.

One batch of the proposed drug product (EED7801) was made at the Daman site ((b) (4) tablets), while the biobatch (BEB3601, manufactured at Baddi) was (b) (4) tablets. The proposed production batch size is (b) (4) tablets.

Comparative dissolution data using the acceptable dissolution method are required to support the additional drug product manufacturing site per the principles of the SUPAC-IR guidance.

Dissolution Method

To support the proposed new drug product manufacturing site per the principles of the SUPAC-IR guidance, the Applicant conducted comparative dissolution testing between the Daman's batch (EED7801) and the biobatch (BEB3601) using the acceptable dissolution method¹:

Acceptable Dissolution Method				
Component	USP Apparatus	Speed (RPMs)	Medium	Volume
Efavirenz	II (Paddle)	100	2% SLS in water	1000 mL
Lamivudine/Tenofovir		75	0.1 N HCl	900 mL

The Applicant provided the comparative dissolution profiles for all three components³. The calculated f_2 value was provided for Efavirenz, but not Lamivudine or Tenofovir due to rapid drug dissolution.

³ <\\cdsesub1\evsprod\nda210649\0008\m3\32-body-data\32p-drug-prod\efa-lami-teno-film-coated-tablets\32p2-pharm-dev\comparative-dissolution-profile-report.pdf>

Drug Component	Dissolution Profiles	f2 Value
Efavirenz	(b) (4)	63.2
Lamivudine		N/A
Tenofovir		N/A
 Reference BEB3601  Test EED7801		

Reviewer's Assessment/ Recommendations:

As shown above, the proposed Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets, 400mg/300mg/300mg manufactured at the proposed additional site (Daman) and the original site (Baddi) have similar dissolution profiles and thus support the proposed new drug product manufacturing site (Daman).

From the Biopharmaceutics perspective, NDA 210649 for Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets, 400mg/300mg/300mg is recommended for **APPROVAL**.



Zhuojun
Zhao

Digitally signed by Zhuojun Zhao

Date: 2/06/2019 03:36:51PM

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Elsbeth
Chikhale

Digitally signed by Elsbeth Chikhale

Date: 2/06/2019 03:47:46PM

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Efavirenz, Lamivudine, and Tenofovir DF Tablets 400mg/300mg/300mg

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)	Based on efavirenz (low solubility)	M		Acc	
Content uniformity	(b) (4)	L		Acc	
Microbial limits		L		Acc	
Dissolution – BCS Class II & IV	Efavirenz has low solubility	M		Acc	
Patient Use Considerations	No instructions for splitting tablets or dispersing in water	L		Acc	



Stephen
Miller

Digitally signed by Stephen Miller

Date: 2/22/2019 03:48:32PM

GUID: 508da7210002a000609476bbeed040f0

Comments: ATL for NDA 210649 Resub-9

Recommendation: [Complete Response](#)

NDA 210649
Review #2 (Resub-8)

Drug Name/Dosage Form	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Strength	400 mg/300 mg/300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Macleods
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resub-8	Mar 15, 2018	Facilities and DS

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Charles Jewell
Drug Product	Yong Wang	Balajee Shanmugam
Process & Microbiology	Christine Falabella	Arwa El Hagrasy
Facility	Daniel DeCiero	Derek Smith
Biopharmaceutics	Zhuojun (Joan) Zhao	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)	(b) (4)	Adequate	Apr 21, 2017	Rev under DMF in Pano
	Type II			Adequate	July 19, 2018	Rev under DMF in Pano
	Type II		(b) (4)	Adequate	Aug 1, 2018	Rev under DMF in Pano
Various	Type III	See DP review				
	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/ucm119231.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

This NDA is recommended for Complete Response from the product quality perspective. There are still outstanding manufacturing risks related to the Macleods Pharmaceuticals Limited - (FEI: 3007517881) manufacturing facility for this NDA. The remaining facilities and other product quality aspects of the application are acceptable at this time.

II. Summary of Quality Assessments

A. Product Overview

This is a resubmission after CR for this three-drug combination tablet containing the lower dose of efavirenz (400mg).

Proposed Indication(s) including Intended Patient Population	Indicated (b) (4) for the treatment of HIV-1 infection in adults and (b) (4) weighing at least (b) (4) kg.
Duration of Treatment	Chronic, until resistance develops.
Maximum Daily Dose	One tablet daily on an empty stomach,
Alternative Methods of Administration	None

B. Quality Assessment Overview

Facilities:

There are still outstanding manufacturing risks related to the Macleods Pharmaceuticals Limited - (FEI: 3007517881) manufacturing facility for this NDA. The remaining facilities are acceptable at this time. An overall Manufacturing Facility Status recommendation of Withhold was entered in to Panorama on Aug 21, 2018. For additional information, see Daniel DeCiero's notes under Inspection View in Panorama, and his facility review in the OPQ Rev-1 dated Mar 13, 2018.

Drug Substance:

Amendments to the three drug substance DMFs were evaluated, and all three are adequate at this time. See Table A on the previous page for the dates of the most recent DMF reviews. For additional information, see Haripada Sarker's drug substance review, below.

Drug Product:

Pink colored, capsule shaped, biconvex film coated tablets debossed with “F 31” on one side and plain on other side. The tablet weighs 1.5 grams. After tightening limit for (b) (4) from NMT (b) (4) % to NMT (b) (4) %, the drug product specification is acceptable. The revised specification, including the revisions to the dissolution procedure, are shown in the “proposed-specifications” document submitted on Feb 21, 2018. Macleods provided an acceptable risk assessment (in 3.2.P.2) showing that all the probable elemental impurities in the drug product are well within the permitted daily exposures under ICH Q3D and USP <232>.

Stability data out to 9 months (Batch BEB3601) and 6 months (remaining 3 batches) were provided, with results supporting the proposed 12-month expiration dating period. The product is proposed to be packaged in three configurations:

- Bottle of 30 tablets with desiccant, induction seal and child-resistant cap
- Bottle of 90 tablets with desiccant, induction seal and child-resistant cap
- Bottle of 180 tablets with desiccant, induction seal and non-child-resistant cap

An in-use study in which the bottle of 180 tablets was opened and sampled four times over the 180-day study duration supported the quality of the tablet as used by patients. For additional information, see Yong Wang’s drug product review in the OPQ Rev-1 dated Mar 13, 2018.

Process:

The proposed drug product is a (b) (4) tablet composed of (b) (4) Efavirenz (400 mg) (b) (4) Lamivudine (300 mg) and Tenofovir Disoproxil Fumarate 300 mg). (b) (4)

(b) (4)

Upon request the applicant revised the in-process controls (b) (4) (b) (4)

(b) (4) The commercial process will use the BEB7701 formulation, at two scales: (b) (4) and (b) (4) tablets. Based on release results, and dissolution comparisons (see Biopharmaceutics section, below), the intended commercial formulation and process is acceptable.

For the release specifications of the finished tablets, the applicant proposed to use (b) (4)

(b) (4) After further justification

including a (b) (4)

(b) (4) the attributes of the drug product specification related to microbial controls were judged to be acceptable. For additional information, see Christine Falabella's process/microbiology review in the OPQ Rev-1 dated Mar 13, 2018.

Biopharmaceutics:

Based on the provided dissolution data, the following revised dissolution methods and acceptance criterion are acceptable and agreed upon:

- Efavirenz: Q= (b) (4)% in 20 min using 2% SLS in water; Apparatus II (paddle) at 100 rpm
- Lamivudine & Tenofovir DF: Q= (b) (4)% in 20 min using 0.1N HCl; Apparatus II (paddle) at 75 rpm

The registration batches (including the Biobatch BEB3601) differ from the proposed commercial batches in terms of the description of the tablets (b) (4)

(b) (4) The Applicant provided adequate comparative dissolution data supporting the bridge between the Biobatch and the commercial image/formulation. For additional information, see Zhuojun (Joan) Zhao's biopharmaceutics review in the OPQ Rev-1 dated Mar 13, 2018.

C. Special Product Quality Labeling Recommendations (NDA only)

The finalization of labeling will be conducted during the next review cycle. The following recommendations from the product quality perspective could be considered at that time:

Prescribing Information:

- 1) Highlights/Dosage Form & Strength: Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg, *for oral use*
- 2) Section 11 - To list all excipients in alphabetical order, the following is recommended:

...., and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, poloxamer, and sodium lauryl sulphate. The tablets are coated with ferric oxide red, hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin.

- 3) Section 16 – add child-resistant cap to descriptions of the bottles of 30, 90 (b) (4) as in:

- Bottle of 30 tablets with silica gel desiccant, (b) (4) induction seal, and child-resistant cap - NDC 33342-362-07

4) Section 16 - Store (b) (4) below 30°C (86°F)

5) Consider whether to add a statement such as “Dispense in original container.”

Container Labels:

6) Would it be appropriate to add any statements such as the following?

- “Keep tightly closed in original container.”
- “This package is child-resistant.” (for the bottles of 30 and 90, if a verification of compliance with 16 CFR 1700 is provided)

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies for Complete Response

I. Facilities Deficiencies

During a recent inspection of the Macleods Pharmaceuticals Limited - (FEI: 3007517881) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.



Stephen
Miller

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Date: 8/27/2018 12:11:24PM

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Comments: ATL for NDA 210649 Resub-8

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Efavirenz, Lamivudine, and Tenofovir DF Tablets 400mg/300mg/300mg

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)	Based on efavirenz (low solubility)	M		Acc	
Content uniformity	(b) (4)	L		Acc	
Microbial limits		L		Acc	
Dissolution – BCS Class II & IV	Efavirenz has low solubility	M		Acc	
Patient Use Considerations	No instructions for splitting tablets or dispersing in water	L		Acc	



Stephen
Miller

Digitally signed by Stephen Miller

Date: 8/27/2018 12:15:43PM

GUID: 508da7210002a000609476bbeed040f0

Comments: ATL for NDA 210649 Resub-8

Recommendation: Complete Response
NDA 210649
Review #1

Drug Name/Dosage Form	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Strength	400 mg/300 mg/300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Macleods
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	Sept 14, 2017	All
Amendment	Oct 18, 2017	Labeling
Amendment	Nov 8, 2017	Quality
Amendment	Jan 5, 2018	Quality
Amendment	Feb 2, 2018	Quality
Amendment	Feb 21, 2018	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Benjamin Stevens Charles Jewell
Drug Product	Yong Wang	Balajee Shanmugam
Process & Microbiology	Christine Falabella	Arwa El Hagrasy
Facility	Daniel DeCiero	Derek Smith
Biopharmaceutics	Zhuojun (Joan) Zhao	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)	Adequate	4/21/2017	Rev under DMF in Pano
	Type II			Adequate	1/18/2017	Rev under DMF in Pano
	Type II			Adequate	9/25/2107	Rev under DMF in Pano
Various	Type III	See DP review				
	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/ucm119231.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

This NDA is recommended for Complete Response from the product quality perspective. There are still outstanding manufacturing risks related to the Macleods Pharmaceuticals Limited - (FEI: 3007517881) manufacturing facility for this NDA. The remaining facilities and other product quality aspects of the application are acceptable at this time.

II. Summary of Quality Assessments

A. Product Overview

This is the second application submitted for this three-drug combination tablet containing the lower dose of efavirenz (400mg).

Proposed Indication(s) including Intended Patient Population	Indicated (b) (4) for the treatment of HIV-1 infection in adults and (b) (4) weighing at least (b) (4) kg.
Duration of Treatment	Chronic, until resistance develops.
Maximum Daily Dose	One tablet daily on an empty stomach,
Alternative Methods of Administration	None

B. Quality Assessment Overview

Facilities:

There are still outstanding manufacturing risks related to the Macleods Pharmaceuticals Limited - (FEI: 3007517881) manufacturing facility for this NDA. The remaining facilities are acceptable at this time. For additional information, see Daniel DeCiero's facility review, below.

Drug Substance:

- (b) (4) was previously reviewed (Review 12) by Manivannan Ethirajan dated 4/21/2017, and was found to be Adequate.
- (b) (4) is recently reviewed (Review-12) by Lauren Woodard dated 01/18/2017, and was found to be Adequate.
- DMF (b) (4) (Tenofovir Disoproxil Fumarate) are reviewed (Review-10) by P. Suresh Jayasekara dated 9/25/2017, and was found to be Adequate.

For additional information, see Haripada Sarker's drug substance review, below.

Drug Product:

Pink colored, capsule shaped, biconvex film coated tablets debossed with “F 31” on one side and plain on other side. The tablet weighs 1.5 grams. After tightening limit for (b) (4) from NMT (b) (4) % to NMT (b) (4) %, the drug product specification is acceptable. The revised specification, including the revisions to the dissolution procedure, are shown in the “proposed-specifications” document submitted on Feb 21, 2018. Macleods provided an acceptable risk assessment (in 3.2.P.2) showing that all the probable elemental impurities in the drug product are well within the permitted daily exposures under ICH Q3D and USP <232>.

Stability data out to 9 months (Batch BEB3601) and 6 months (remaining 3 batches) were provided, with results supporting the proposed 12-month expiration dating period. The product is proposed to be packaged in three configurations:

- Bottle of 30 tablets with desiccant, induction seal and child-resistant cap
- Bottle of 90 tablets with desiccant, induction seal and child-resistant cap
- Bottle of 180 tablets with desiccant, induction seal and non-child-resistant cap

An in-use study in which the bottle of 180 tablets was opened and sampled four times over the 180-day study duration supported the quality of the tablet as used by patients. For additional information, see Yong Wang’s drug product review, below.

Process:

The proposed drug product is a (b) (4) tablet composed of (b) (4) Efavirenz (400 mg) (b) (4) Lamivudine (300 mg) and Tenofovir Disoproxil Fumarate 300 mg). (b) (4)
(b) (4)

(b) (4)

Upon request the applicant revised the in-process controls (b) (4)
(b) (4)

(b) (4)
(b) (4)

(b) (4) The commercial process will use the BEB7701 formulation, at two scales: (b) (4) and (b) (4) tablets. Based on release results, and dissolution comparisons (see Biopharmaceutics section, below), the intended commercial formulation and process is acceptable.

For the release specifications of the finished tablets, the applicant proposed to use

(b) (4)

(b) (4) After further justification

including a

(b) (4)

, (b) (4) the attributes of the drug product specification related to microbial controls were judged to be acceptable. For additional information, see Christine Falabella's process/microbiology review, below.

Biopharmaceutics:

Based on the provided dissolution data, the following revised dissolution methods and acceptance criterion are acceptable and agreed upon:

- Efavirenz: $Q = \frac{(b)(4)}{(4)}\%$ in 20 min using 2% SLS in water; Apparatus II (paddle) at 100 rpm
- Lamivudine & Tenofovir DF: $Q = \frac{(b)(4)}{(4)}\%$ in 20 min using 0.1N HCl; Apparatus II (paddle) at 75 rpm

The registration batches (including the Biobatch BEB3601) differ from the proposed commercial batches in terms of the description of the tablets (b) (4)

(b) (4) The Applicant provided adequate comparative dissolution data supporting the bridge between the Biobatch and the commercial image/formulation. For additional information, see Zhuojun (Joan) Zhao's biopharmaceutics review, below.

C. Special Product Quality Labeling Recommendations (NDA only)

The finalization of labeling will be conducted during the next review cycle. The following recommendations from the product quality perspective could be considered at that time:

Prescribing Information:

- 1) Highlights/Dosage Form & Strength: Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 400 mg/300 mg/300 mg, *for oral use*
- 2) Section 11 - To list all excipients in alphabetical order, the following is recommended:

...., and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, poloxamer, and sodium lauryl sulphate. The tablets are coated with ferric oxide red, hydroxypropyl methylcellulose, lactose monohydrate, titanium dioxide, and triacetin.

- 3) Section 16 – add child-resistant cap to descriptions of the bottles of 30, 90 (b) (4) as in:

- Bottle of 30 tablets with silica gel desiccant, (b) (4) induction seal, *and child-resistant cap* - NDC 33342-362-07

4) Section 16 - Store (b) (4) below 30°C (86°F)

5) Consider whether to add a statement such as “Dispense in original container.”

Container Labels:

6) Would it be appropriate to add any statements such as the following?

- “Keep tightly closed in original container.”
- “This package is child-resistant.” (for the bottles of 30 and 90, if a verification of compliance with 16 CFR 1700 is provided)

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies for Complete Response

I. Facilities Deficiencies

During a recent inspection of the Macleods Pharmaceuticals Limited - (FEI: 3007517881) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

Stephen P. Miller, Ph.D.

Application Technical Lead for NDA 210649



Stephen
Miller

Digitally signed by Stephen Miller

Date: 3/13/2018 10:30:38AM

GUID: 508da7210002a000609476bbeed040f0

BIOPHARMACEUTICS**Product Background:****NDA:** 210649 (505(b)(2)).**Drug Product Name / Strength:** Efavirenz, Lamivudine and Tenofovir disoproxil fumarate IR Tablets, 400mg/300mg/300mg**Route of Administration:** Oral**Applicant Name:** Macleods Pharmaceuticals Limited**Review Summary:**

This NDA is filed under the U.S. President's Emergency Plan for AIDS Relief, PEPFAR. The intended indication is for the treatment of human immune-deficiency virus (HIV-1) (b) (4). One strength, 400 mg/300 mg/300 mg (Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate) is proposed in the current application.

(b) (4)

This New Drug Application is submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355). The listed drugs are the individual components drug products Sustiva® (efavirenz) tablets 600 mg, EPIVIR® (lamivudine) Tablets 300 mg and VIREAD® (tenofovir disoproxil fumarate) tablets 300 mg. The clinical basis for this NDA is the demonstration of bioequivalence of the Applicant's proposed product (Efavirenz/Lamivudine/Tenofovir Disoproxil Fumarate Tablets, 400/300/300 mg) to the individual listed drugs Epivir® 300 mg tablets , Viread® 300 mg tablets and the reduced efavirenz 400 mg (two Mylan's Efavirenz tablets, 200mg) per the Division of Antiviral Products' requirements communicated to the Applicant on December 10, 2016¹.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method and acceptance criteria and evaluation of the bridge between the commercial drug product and the drug product used in the BE studies.

Based on the provided dissolution data, the following revised dissolution method and acceptance criterion are acceptable and agreed upon:

Acceptable Revised Dissolution Method and Acceptance Criterion					
Component	USP Apparatus	Speed (RPMs)	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
Efavirenz	II (Paddle)	100	2% SLS in water	1000 mL	NLT (b) (4) % (Q) in 20 minutes
Lamivudine/ Tenofovir		75	0.1 N HCl	900 mL	

¹ \\cdsesub1\evsprod\nda210649\0000\m1\us\1-2-cover-letters\division-antiviral-agents-email.pdf

The registration batches (including the Biobatch BEB3601) differ from the proposed commercial batches in terms of the description of the tablets (b) (4)

The Applicant provided adequate comparative dissolution data supporting the bridge between the Biobatch and the commercial image/formulation.

From the Biopharmaceutics perspective, NDA 2010649 for Efavirenz, Lamivudine and Tenofovir disoproxil fumarate IR Tablets, 400mg/300mg/300mg is recommended for **APPROVAL**.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original Submission	6/26/2017
IR Response	1/5/2018
IR Response	2/21/2018

BCS Designation

The Applicant did not request an official BCS designation.

Drug Substance Solubility:

Solubility of the drug substances are provided as shown below:

Table 1 Solubility Profiles of Drug Substance at 37°C

Efavirenz	Aqueous buffer solution	Solubility (mg/mL)	Inference as per USP			
	pH 1.2	0.00330	Practically Insoluble			
	pH 2.0	0.00305	Practically Insoluble			
	pH 3.0	0.00273	Practically Insoluble			
	pH 4.0	0.00336	Practically Insoluble			
	pH 4.5	0.00325	Practically Insoluble			
	pH 5.0	0.00242	Practically Insoluble			
	pH 6.0	0.00299	Practically Insoluble			
	pH 6.8	0.00209	Practically Insoluble			
	pH 7.0	0.00276	Practically Insoluble			
	pH 8.0	0.00288	Practically Insoluble			
Water	0.00245	Practically Insoluble				
Lamivudine	Batch No. of Lamivudine	Volume of water required				
		pH 1.2	pH 4.8	pH 6.8	pH 9.18	
	DBH010-4-B15B-110813b	4 mL	8 mL	8 mL	9 mL	
	DBH010-4-B15B-110814b	4 mL	8 mL	8 mL	9 mL	
	DBH010-4-B15B-110815b	4 mL	8 mL	8 mL	9 mL	
	Conclusion	Freely soluble	Freely soluble	Freely soluble	Freely soluble	

Tenofovir Disoproxil Fumarate	Buffer solution	Solubility (mg/250 mL)
	Hydrochloric acid buffer pH 1.0	312.10
	Acetate buffer pH 4.5	300.60
	Phosphate buffer pH 6.91	288.27
	Phosphate buffer pH 7.5	313.83
	Phosphate buffer pH 7.91	316.27
	Borate buffer pH 8.91	254.70

Permeability:

No data are provided.

Drug Substances:**Efavirenz**

Efavirenz exhibits polymorphism. The polymorphic form used in the proposed drug product is (b) (4). The Applicant uses DSC and pXRD to confirm the polymorphic form.

Lamivudine

Lamivudine exists in two polymorphic forms, (b) (4) (b) (4) is used for the preparation of the proposed drug product, demonstrated by the observed melting point, IR spectra, DSC, and X-ray powder diffraction patterns.

Tenofovir Disoproxil Fumarate

Tenofovir Disoproxil Fumarate exhibits polymorphism. The Applicant states that (b) (4) is used for the preparation of the proposed drug product (b) (4)

(b) (4)

Formulation:

The proposed drug product is a film coated (b) (4) tablet, (b) (4) (b) (4)

Table 2: Unit Composition for the Commercial Batch

(b) (4)



(b) (4)

Dissolution Method

The Applicant initially proposed to use [REDACTED] (b) (4)

[REDACTED] The Applicant did not provide results of step-wise experiments or any justification for the choice of dissolution apparatus, dissolution medium, and agitation speed in the Pharmaceutical Development Report ([Module 3.2.P.2](#)). [REDACTED] (b) (4)

In the Biopharmaceutics Information Requests dated 12/22/2017 ([Appendix I](#)), the Applicant was requested to develop two dissolution methods, one method for the highly insoluble component Efavirenz and one method without surfactant for Lamivudine and Tenofovir. [REDACTED] (b) (4)

(b) (4)

The newly proposed revised dissolution methods:

Drug Product	Dissolution method	
	Efavirenz	Lamivudine and Tenofovir
Apparatus	USP II (Paddle)	
Rotation (rpm)	100	75
Medium	2% SLS in water	0.1 N HCl
Volume (mL)	1000	900

Dissolution Method Validation:

The Applicant provided the validation report for the original proposed dissolution method. The revised dissolution method validation was found acceptable for (b) (4).

Discriminating Power of the Method: Not Provided**Reviewer's Assessment:**

Based on the provided information in the IR response dated 1/5/2018 (Appendix I) (b) (4)

(b) (4)
(b) (4) the revised dissolution methods are acceptable.

Dissolution Acceptance Criterion:

The originally proposed dissolution acceptance criteria were recommended for revision as shown in Appendix II. Based on the provided dissolution data using the revised dissolution methods, the following revised acceptance criterion was found acceptable and agreed upon for all components:

Cumulative % of Drug Dissolved (Label Claim)
NLT (b) (4) % (Q) in 20 minutes

Bridging of Formulations:

Macleods has manufactured 3 registration batches, which differ from the proposed commercial batches in terms of the description of the tablets and (b) (4)

(b) (4)

The Description difference (b) (4) between the registration batches and proposed commercial drug product is shown below:

Results			
BEB3601	BEB3602	BEB3603	BEB7701

(b) (4)

(b) (4)

The difference (b) (4) between registration batches and proposed commercial drug product is shown below:

BEB3601/BEB3602/BEB3603	(b) (4)
BEB7701	

To support the changes between the registration (and bio-) batch formulation and the proposed commercial formulation in the description (b) (4) of the tablets (b) (4) (b) (4) the Applicant has manufactured an additional exhibit batch (BEB7701) with the proposed commercial description and formulation. The Applicant provided the following comparative dissolution profiles comparing the Biobatch and the exhibit batch using the acceptable revised dissolution method.

Drug Component	Batch #	Cumulative % of Drug Dissolved (Label Claim)
Efavirenz	BEB3601 (Biobatch)	(b) (4)

Drug Component	Batch #	Cumulative % of Drug Dissolved (Label Claim)
	BEB7701 (proposed commercial formulation)	(b) (4)
Lamivudine	BEB3601 (Biobatch)	(b) (4)
	BEB7701 (proposed commercial formulation)	(b) (4)
Tenofovir Disoproxil Fumarate	BEB3601 (Biobatch)	(b) (4)

Drug Component	Batch #	Cumulative % of Drug Dissolved (Label Claim)
	BEB7701 (proposed commercial formulation)	(b) (4)

Reviewer's Assessment:

The comparative dissolution data support the similarity between the two formulations (b) (4)

f2 values (calculated by this reviewer)	
Efavirenz	94.45
Lamivudine	N/A (both profiles exhibit more than (b) (4)% drug dissolved at (b) (4) minutes)
Tenofovir Disoproxil Fumarate	

The change in (b) (4) do not have a detectable impact on the drug product's dissolution profiles. Therefore, these dissolution data support the bridge between the biobatch and the commercial image/formulation.

R Regional Information

Comparability Protocols: None

Post-Approval Commitments: None

Lifecycle Management Considerations: None

List of Deficiencies: None

Recommendations:

From the Biopharmaceutics perspective, NDA 2010649 for Efavirenz, Lamivudine and Tenofovir disoproxil fumarate IR Tablets, 400mg/300mg/300mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Joan Zhao, Ph.D. 2/22/2018

Secondary Reviewer Name and Date: Elsbeth Chikhale, Ph.D. 2/23/2018

APPENDIX I: Biopharmaceutics Information Requests dated 12/22/2017 and Applicant's Response dated 1/5/2018

Biopharmaceutics Request Comments:

1. The proposed dissolution method appears not suitable for your drug product which contains API's with markedly different physicochemical properties and therefore is not acceptable.

Your proposed fixed-dose combination product should be subjected to two different dissolution methods. Develop and validate one method utilizing a dissolution medium with surfactant for Efavirenz, the highly insoluble component, and another method (without surfactant) for Lamivudine and Tenofovir.

(b) (4) provide dissolution data using the following dissolution methods to explore if these two dissolution methods are appropriate for your proposed drug product:

Drug Component	USP Apparatus	Rotation Speed	Medium	Volume
Efavirenz	USP II (Paddle)	(b) (4)	2% SLS in water	1000 mL
Lamivudine and Tenofovir			0.1 N HCl	900 mL

For both methods, the dissolution profile(s) for all 4 registration batches (BE3601, BEB3602, BEB3603 and BEB7701) should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve (12) samples per testing.

2. Provide data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes and critical process parameters (i.e., (b) (4)% change to the specification-ranges of these variables).
3. Include a detailed discussion of the justification of the proposed dissolution acceptance criteria. The selection of the specification time point should be where $Q = (b) (4)\%$ dissolution occurs.

Applicant's Response to Biopharmaceutics-IR Comments 1-3:

We acknowledge the Agency's concerns on media, parameters, specification and discriminatory ability of proposed dissolution methodology for the drug product.

(b) (4)

(b) (4)

Drug Component	USP Apparatus	Rotation speed	Medium	Volume	Specification
Efavirenz	USP II (Paddle)	100 RPM	2% SLS in Water	1000 ml	(b) (4) % (Q) in (b) (4) min
Lamivudine and Tenofovir		75 RPM	0.1 N HCl	900 ml	(b) (4) % (Q) in 20 min

To address Agency's concerns, we would like to propose above same dissolution methodology and specification for proposed new product i.e. Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 400 mg / 300 mg / 300 mg.

Report for dissolution profile of all 4 submission batches (BEB3601, BEB3602, BEB3603 and BEB7701) with above methodology is provided under section m2-7-clinical-summary.

A copy of proposed drug product specification is provided under section m3-2-p-5-1-specifications.

Reviewer Note:

(b) (4)

The Applicant provided the dissolution profiles for all 4 exhibit batches using the revised dissolution method(s). All exhibit batches are within the proposed expiration date at the time of testing.

Batch #	Mfg. Date	Testing Date	Age (month)
BEB3601	April 2016	Jan 2018	22
BEB3602	June 2016		20
BEB3603	June 2016		20
BEB7701	April 2017		14

Drug Component	Batch #	Cumulative % of Drug Dissolved (Label Claim)
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Drug Component	Batch #	Cumulative % of Drug Dissolved (Label Claim)
Efavirenz	BEB3601 (Biobatch)	(b) (4)
	BEB3602	
	BEB3603	
	BEB7701 (proposed commercial formulation)	

Drug Component	Batch #	Cumulative % of Drug Dissolved (Label Claim)
Lamivudine	BEB3601 (Biobatch)	(b) (4)
	BEB3602	
	BEB3603	
	BEB7701 (proposed commercial formulation)	

Drug Component	Batch #	Cumulative % of Drug Dissolved (Label Claim)
Tenofovir Disoproxil Fumarate	BEB3601 (Biobatch)	(b) (4)
	BEB3602	
	BEB3603	
	BEB7701 (proposed commercial formulation)	

Based on the above data, the following acceptance criteria are recommended:

<i>Drug Component</i>	Acceptance Criteria Cumulative % of Drug Dissolved (Label Claim)
<i>Efavirenz</i>	<i>NLT</i> (b)(4) % (Q) in 20 minutes
<i>Lamivudine and Tenofovir</i>	<i>NLT</i> (b)(4) % (Q) in (b)(4) minutes

APPENDIX II: *Biopharmaceutics Information Requests dated 2/14/2018 and Applicant's Response dated 2/21/2018*

Biopharmaceutics Request Comments:

1. Based on the submitted dissolution data in your IR response dated January 5, 2018, the following dissolution acceptance criteria are recommended for your proposed drug product:

Drug Component	Acceptance Criteria
	Cumulative % of Drug Dissolved (Label Claim)
Efavirenz	NLT ^{(b) (4)} % (Q) in 20 minutes
Lamivudine and Tenofovir	NLT ^{(b) (4)} % (Q) in ^{(b) (4)} minutes

Note that the setting of the dissolution acceptance criterion is based on mean values (n=12) and, therefore, some batches may require stage 2 and occasionally stage 3 testing.

2. Provide an updated Specifications table for the Drug Product with the revised acceptance criteria for the dissolution test.

Applicant's Response to Biopharmaceutics-IR Comment 1:

We acknowledge the Agency's concerns on dissolution acceptance criteria for the proposed formulation of Efavirenz, Lamivudine and Tenofovir disoproxil fumarate Tablets 400 mg / 300 mg / 300 mg

(b) (4)

(b) (4)

(b) (4)



Hence, based on the above justification we request Agency to consider the following dissolution acceptance criteria for proposed formulation of Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets 400 mg / 300 mg / 300 mg.

Drug Component	Acceptance Criteria Cumulative % of Drug Dissolved (Label Claim)
Efavirenz	NLT (b) (4)% (Q) in 20 minutes
Lamivudine and Tenofovir	NLT (b) (4)% (Q) in 20 minutes

Reviewer Note:

The Applicant's response is satisfactory. The revised acceptance criterion of NLT (b) (4)% (Q) in 20 minutes for Lamivudine and Tenofovir is justified and acceptable.

Applicant's Response to Biopharmaceutics-IR Comment 2:

We acknowledge Agency's comment. In view of the response to the above deficiency point no. 3, updated proposed specifications table for the Drug Product with the revised acceptance criteria for the dissolution test is provided under section [m3-2-p-5-1](#).

Reviewer Note:

The Applicant's response is satisfactory.



Zhuojun
Zhao

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Elsbeth
Chikhale

Digitally signed by Elsbeth Chikhale

Date: 2/23/2018 09:43:43PM

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Final Risk Table for Efavirenz, Lamivudine, and Tenofovir DF Tablets 400mg/300mg/300mg

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)	Based on efavirenz (low solubility)	M		Acc	
Content uniformity	(b) (4)	L		Acc	
Microbial limits		L		Acc	
Dissolution – BCS Class II & IV	Efavirenz has low solubility	M		Acc	
Patient Use Considerations	No instructions for splitting tablets or dispersing in water	L		Acc	



Stephen
Miller

Digitally signed by Stephen Miller

Date: 3/13/2018 10:31:07AM

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