CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022343Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 22343

Review #1 (for full approval request)

Drug Name/Dosage Form	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Strength	600 mg/300 mg/300 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Aurobindo Pharma Limited
US agent, if applicable	Ms. Blessy Johns, Aurobindo Pharma USA, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Seeking full approval	*2/15/2018*	
Amendment	*10 APR 2018*	*List of post TA changes*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	David Claffey	Charles Jewell
Drug Product		Balajee Shanmugam
Process		
Microbiology		
Executive Summary		
Facility	Derek Smith	
Regulatory Business Process Manager	Luz Rivera	
Application Technical Lead	Stephen Miller	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

One site for each of the actives was approved in the orginal TA for this application. Since then two additional sites were approved for Efavirenz: Aurobindo Unit-X1 in S-3 in 2014 (DMF (b) (4)) and (b) (4) in S-2 in 2014 (DMF (b) (4)).

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	Aurobindo Pharma Limited, Unit-VIII	Efavirenz usp	3	Adequate	11/3/2017	Reviewed by Manivannan Ethirajan. Only 2017 AR submitted on 11/22/2017 NAI
	II	**Aurobindo Pharma Limited, Unit-XI**	Efavirenz	3	Adequate	10/18/2017	D Skacnky **site approved as part of Supplement S-3 in 2014**
	II	(b) (4)		3	Adequate	3/24/2017	Manivannan Ethirajan. No further updates. Site approved as part of S.2 in 2014.
	II	Aurobindo Pharma Limited, Unit-XI	Lamivudine	3	Adequate	2/2/2018	Reviewed by Hari Sarker (4 MAY 2018)

(b) (4)	II	Aurobindo Pharma Limited, Unit-XI	Tenofovir Disoproxil Fumarate	3	Adequate	1/27/2017	Reviewed by Ying Lin (only administrative amendment and ARs since that date. GDUFA no further comments letter sent on 26 JAN 2018. Only agent change amendment since that date.

	IV	(b) (4)	4			
(b) (4)	IV		4			
	IV		4			
	IV		4			
	IV		4	N/A	N/A	Comment in review.
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4			
	III		4	N/A	N/A	Comment in review.
	III		4	N/A		Comment in review.

3=reviewed and found acceptable. 4=adequate information provided in application to support its use

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22142	Approved (2018) -ELT Tablet of same strength
Tentatively Approved NDAs for ELT Tablet of the same strength are listed in this public database:	http://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm	

2. CONSULTS: None

Executive Summary

Recommendations and Conclusion on Approvability

Recommend final approval of this application from a product quality perspective. The application was tentatively approved in 2013. Eight supplements were subsequently submitted and found acceptable. The referenced DMFs were reevaluated during this review cycle and remain adequate to support this application. The drug substance and drug product manufacturing and testing sites were found to be acceptable on 22 JUN 2018 by OPQ OPF.

I. Summary of Quality Assessments

A. Product Overview

The proposed drug product, Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a single dosage strength film-coated bilayer tablet. The strength is labeled in terms of the three actives 600mg, 300mg and 300 mg, respectively. The original application received a tentative approval (TA) on 26 JUN 2013. A list of all changes made since the tentative approval was submitted in the 10 April 2018 amendment, and this information is included below. One site for each of the actives was approved in the original TA for this application. Since then two additional sites were approved for Efavirenz: Aurobindo Unit-X1 in S-3 in 2014 (DMF (b) (4)) and (b) (4) in S-2 in 2014 (DMF (b) (4)). All the current referenced DMFs and manufacturing sites were found to be acceptable.

0	⇦ **Total Number of Comparability Protocols (ANDA only)**

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 40 kg
Duration of Treatment	***Chronic***
Maximum Daily Dose	Recommended dose: One tablet (containing 600 mg of efavirenz, 300 mg of lamivudine and 300 mg of tenofovir disoproxil fumarate) taken once daily orally on an empty stomach, preferably at bedtime.
Alternative Methods of Administration	***None.***

B. Quality Assessment Overview

DRUG SUBSTANCEs: The drug product contains three drug substances, one non-nucleoside reverse transcriptase inhibitor (efavirenz) and two nucleo(t)side reverse transcriptase inhibitors (lamivudine and tenofovir disoproxil fumarate). All their associated DMFs were recently found acceptable to support NDAs or ANDAs. The following summarizes the updates to the DMFs associated with these actives since the original TA action for this application.

Lamivudine drug substance (DMF (b) (4)): DMF (b) (4) is referenced by the lamivudine DMF (b) (4) for the (b) (4) It was found adequate by Deborah Johnson on 18 APR 2018 (not for entire DMF which is for lamivudine, but just for (b) (4) DMF (b) (4)).

DMF (b) (4) is also referenced by DMF (b) (4) – also as a source of the lamivudine (b) (4). It was found adequate in review #3 to support DMF (b) (4) with respect to the review of NDA 22344 by Hari Sarker on 4 MAY 2018. The prior review found that DMF (b) (4) was inadequate – however this was in relation to the use of the (b) (4)
Subsequently Hari Sarker found DMF (b) (4) adequate to support NDA 22344 on 4 MAY 2018 (Review #14) after the prior two reviews found it inadequate due to deficiencies stated above for DMF (b) (4). This reviewer concurs with the adequate finding of DMF (b) (4) in relation to its support of this application.

Efavirenz drug substance (DMFs (b) (4)): One site for Efavirenz drug substance was included when this application was originally TA'ed – Aurbindo Pharma. Its associated DMF (b) (4) was found adequate on 3 NOV 2018 (no amendments have been submitted since that time). Since the original TA action, two additional efavirenz drug substance sites were the subject of two supplements. Supplement 2 was approved in 2014 for the addition of (b) (4) as an efavirenz manufacturing site. Its associated DMF (b) (4) was most recently found adequate on 24 MAR 2017 (no subsequent updates). Supplement 3 was approved in 2014 for the addition of Aurobindo Pharma Unit-X1 drug substance site. Its associated DMF (b) (4) was most recently found adequate on 18 OCT 2017. There is one manufacturing site associated with each efavirenz DMF. Each was checked to ensure that there were no additional upstream manufacturing sites which may carry out GMP steps – there appeared to be none.

Tenofovir Disoproxil Fumarate drug substance (DMF (b) (4)): The one site found acceptable in the original TA'ed application remains acceptable – as does its referenced DMF (b) (4) (27 JAN 2017).

DRUG PRODUCT:
The proposed drug product, Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets is a single dosage strength film-coated bilayer tablet. The strength

is labeled in terms of the three actives 600mg, 300mg and 300 mg, respectively. The applicant stated that they do not plan to use a proprietary name at this time. The bilayer tablet (b) (4) They are white, oval, bevel edged, biconvex, film-coated tablets.
Only the tenofovir disoproxil component is present as a salt. 300 mg of tenofovir disoproxil fumarate is equivalent to 245 mg of tenofovir disoproxil. The tablets are embossed with an "I" on one side and "91" on the other. The drug product is manufactured at Aurobindo Pharma Limited, Unit-VII. The current drug product specification is attached to this review for reference.
The tablets also include the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, ferric oxide, hypromellose, magnesium stearate.

The applicant proposes marketing the tablets in HDPE bottles as 30 count, and 90 count with child resistant closures and heat sealed liner, and (b) (4) desiccant. Approval for a 90-count HDPE bottle with child resistant closure was sought in Supplement-8 after submission of this request for full approval. Supplement-8 included in-use stability data and was found acceptable by Alan Fenselau (27 MAY 2018). A PEPFAR-Permitted letter was issued on 5 JULY 2018. The 14 MAY 2018 amendment includes a description of all packaging configurations, including the bottles of (b) (4) count tablets that are tentatively approved. However, the 9 MAR 2018 amendment clarified that the only packaging configurations that will be marketed going forward are the 30- and 90-count configurations.

Stability data support the proposed "Store below 30°C" conditions. An expiry period of 24 month was granted with the initial TA action. The postmarketing stability protocol stated that the "expiration dates may be extended based upon long term stability data from a minimum of three production batches." However, the applicant confirmed (15 JUN 2015 amendment) that the drug product expiry period remains at 24 months.

The applicant provided an elemental impurities risk assessment report. The data supported the claim that all elemental impurities present in the drug substance, excipients, packaging components and manufacturing equipment comply with ICH Q3D (b) (4) The applicant committed to reassessing compliance with changes to drug substance, excipient, packaging or equipment postmarketing changes.

Following an assessment of the final proposed commercial manufacturing facilities, (b) (4) OPF found that there are no outstanding compliance issues or residual risks. The application is recommended for approval from the Facility perspective on 22 JUN 2018.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

APPEARS THIS WAY ON ORIGINAL

Review Notes

CURRENT DRUG PRODUCT Specification (From 2016 Annual Report):

(b) (4)

(b) (4)

List of changes made after TA action (provided in 10 APR 2018 amendment after agency request.

S. No.	Amendment Received date	Proposed Changes	Amendment Status
1	September 13, 2013	**Chemistry amendment:** Revision in efavirenz drug substance specification and test procedure in-line with current USP monograph, and accordingly revision in drug product (Efavirenz tablets) specification and test procedure	Permitted on March 13, 2014

S. No.	Amendment Received date	Proposed Changes	Amendment Status
2	December 12, 2013	**Prior Approval Amendment:** 1) Introduction of an alternate source (b) (4) (b) (4) DMF (b) (4)) of Efavirenz, USP. 2) Introduction of an alternate manufacturing process for Tenofovir Fumarate drug substance in addition to the existing manufacturing process. 3) Introduction of an alternate source for the packaging component of bulk shipment pack (i.e., (b) (4) in addition to the existing source).	Permitted on April 11, 2014
3	January 08, 2014	**CBE-30 Amendment:** Introduction of an alternate manufacturing facility (i.e. M/s Aurobindo Pharma Limited, Unit-XI) for Efavirenz USP drug substance.	Permitted on May 07, 2014
4	July 21, 2014	**CBE-30 Amendment:** Revision in the specification of Croscarmellose Sodium excipient in-line with current USP-NF monograph	Permitted on December 16, 2014
5	January 06, 2015	**CBE-30 Amendment:** Revision to Lamivudine, USP drug substance specification and test procedure, as amended in DMF # (b) (4) in order to be in-line with the current USP monograph.	Permitted on July 06, 2015
	June 23, 2015	IR Amendment dated June 16, 2015: Based on the agency's comment, provided LOA for DMF # (b) (4)	
6	June 12, 2015	**CBE-30 Amendment:** Revision to the specification and test procedure of Hydroxypropyl Cellulose excipient in order to be aligned with current USP-NF monograph	Permitted on December 08, 2015
7	August 04, 2016	**CBE-30 Amendment:** Addition of an alternate supplier (b) (4) (b) (4)	
	August 26, 2016	IR Drug Product Quality Review amendment: Based on the agency's comment, updated 356h form and Module 3 for additional facility provided as per the DMF holder	

S. No.	Amendment Received date	Proposed Changes	Amendment Status
	September 30, 2016	Amendment dated September 19, 2016: Based on the agency's comment, an alternate testing facility of the drug substance TDF as amended in DMF # (b) (4)	Permitted on February 02, 2017
	January 16, 2017	IR Drug Product Quality Review amendment: DMF holder shall revise the specification of (b) (4) (b) (4)	
8	August 09, 2016	**General Correspondence:** Bio-analytical laboratory closure information, where the bio-analytical phase of the fasting BE study of this NDA was conducted.	Not applicable
9	June 06, 2017	Submission of Initial Pediatric Study Plan	Not applicable
10	January 05, 2018	**CBE-30 Amendment:** Inclusion of new container pack i.e., 90's count HDPE container	Under review
	March 09, 2018	IR amendment: Information provided for commercialization of counts (30's, 90's (b) (4)) bottles.	

Evaluation: PEPFAR-Permitted letters were issued after review of each change, including the last CBE-30 amendment (on 5 JUL 2018).

David Claffey

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Stephen Miller

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Efavirenz, Lamivudine and Tenofovir Disoproxil Fumarate Tablets
Dosage form, route of administration	Tablets, for oral use
Controlled drug substance symbol (if applicable)	n/a
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 600 mg efavirenz, 300 mg lamivudine and 300 mg tenofovir disoproxil fumarate

2. *Section 2 Dosage and Administration*

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)	No special instructions. one tablet per day taken orally on an empty stomach, preferably at bedtime.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets
Strengths: in metric system	Efavirenz, Lamivudine and Tenofovir disoproxil fumarate are available as tablets. Each tablet contains 600 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 (which is equivalent to 245 mg of tenofovir disoproxil).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Not described in this section

Section 11 DescriptionItem	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	No proprietary name has been proposed so just states non proprietary name
Dosage form and route of administration	States it is a fixed dose combination in a film coated bilayered tablet.
Active moiety expression of strength with equivalence statement (if applicable)	Yes. States that 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>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Yes. Efavirenz is an HIV-1 specific, non-nucleoside, reverse transcriptase inhibitor (NNRTI). Lamivudine is a synthetic nucleoside analogue Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. *In vivo* tenofovir disoproxil fumarate 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	Yes for all three.
If radioactive, statement of important nuclear characteristics.	

Other important chemical or physical properties (such as pKa or pH)	Yes.

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

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 600 mg/300 mg/300 mg are supplied in HDPE bottles as 30 count , (b) (4) (with child resistant closure) and (b) (4) , both with heat sealed liner and (b) (4) desiccant.
Available units (e.g., bottles of 100 tablets)	Bottles of 30 NDC 65862-722-30 (b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not present. Needs to be included.
Special handling (e.g., protect from light)	None
Storage conditions	**Store below 30°C.**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes. Distributed by: Aurobindo Pharma USA, Inc. 279 Princeton-Hightstown Road East Windsor, NJ 08520 Manufactured by: Aurobindo Pharma Limited Hyderabad-500 038, India

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

Complies with CMC related regulatory requirements. Will need to add tablet description to section 16. "white, oval, bevel edged, biconvex, film-coated tablets" The

tablets are embossed with an "I" on one side and "91" on the other. The details of the 90-count will also need to be added to Section 16. This configuration was found acceptable in Supplement-8 on 5 JULY 2018. The 14 MAY 2018 amendment includes a description of all packaging configurations, including the bottles of (b) (4) that are tentatively approved. However, the 9 MAR 2018 amendment clarified that the only packaging configurations that will be marketed going forward are the 30- and 90-count configurations.

II. Labels:

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

(b) (4)

2. ***Carton Label***

(b) (4)

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))	Appropriate. There is no proprietary name, so non-proprietary name is adequately prominent.	
Dosage strength	Yes.	yes
Net contents	yes	yes
"Rx only" displayed prominently on the main panel	yes	yes
NDC number (21 CFR 207.35(b)(3)(i))	yes	yes
Lot number and expiration date (21 CFR 201.17)	Yes in box	yes
Storage conditions	yes	yes
Bar code (21CFR 201.25)	yes	yes
Name of manufacturer/distributor	yes	yes
And others, if space is available		

Reviewer's Assessment of Labels: *{Adequate }*
The labels comply with all regulatory requirements from a CMC perspective and contain the same cmc-related information as the PI. Although the (b) (4) bottles are tentatively approved, the 9 MAR 2018 amendment clarified that the only packaging configurations that will be marketed going forward are the 30- and 90-count configurations. The PI will need to be amended to reflect this.

List of Deficiencies: None. The changes listed above will be made the PI.

Overall Assessment and Recommendation: Acceptable.

Primary Labeling Reviewer Name and Date:

David Claffey, 28 JUL 2018

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

Balajee Shanmugam JUL 2018.

David Claffey

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Balajee Shanmugam

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David Claffey

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Stephen Miller

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