CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204311Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMO

DATE: December 22, 2023

TO: NDA 204311

FROM: David Claffey, Ph.D.

SUBJECT: Storage statement and CR containers in drug labeling

The Applicant resubmitted NDA 204311 for Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg for final approval after receiving tentative approval in 2014. FDA's current practice for approved products is to use a standard USP storage statement in labeling and for PEPFAR products is to use 'store below 30ºC'. For a product such as this, which is stored at room temperature and will have final approval, our current practice is to use '20ºC to 25ºC'. In discussions with USAID, they indicated this product would be excluded from use in the PEPFAR program if the labeling included the standard USP room temperature statement. This is because these products are used in countries where storage at room temperature is not always possible. Therefore, I recommend that the labeling for this product include a storage statement of store below 30ºC (86ºF). This is scientifically justified, as the application includes stability data to support this statement. This will allow continued access of this product to all patients.

Note that the application includes both child-resistant (CR) and non-child-resistant caps for the container closure system. Both were found acceptable from a product quality perspective. The currently approved labeling includes only child-resistant packaging which is in line with the requirements for products marketed in the US.

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/s/

DAVID J CLAFFEY
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NDA Executive Summary

1. Application/Product Information

NDA Number.	204311
Applicant Name	Mylan Laboratories Limited
Drug Product Name	Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg
Dosage Form.	Tablet, for suspension
Proposed Strength(s)	Abacavir: 60 mg Lamivudine: 30 mg
Route of Administration	Oral
Maximum Daily Dose	600 mg abacavir; 300 mg lamivudine
Rx/OTC Dispensed	Rx
Proposed Indication	It is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients aged 3 months and older or weighing at least 5 kg.
Drug Product Description	White to off white, round, (b) (4) tablet debossed with AL above the score and 7 below the score on one side and M on the other side of the tablet. The tablets contain two active pharmaceutical ingredients in a fixed-dose combination: 60 mg abacavir and 30 mg of lamivudine. The recommended dosage is based on weight (should not exceed 10 tablets per day). The tablets are proposed to be packaged in 60-count HDPE bottles with an induction seal and child-resistant caps for US commercial supply. The tablets are also proposed to be packaged in 60-count HDPE bottles with an induction seal and non-child-resistant screw cap for use in PEPFAR countries.
Co-packaged product information	N/A
Device information:	N/A
Storage Temperature/ Conditions	(b) (4)

Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Not assigned this review cycle	
	Drug Product/ Labeling	Hudson Roth	David Claffey
	Manufacturing	Chunsheng Cai	Bo Jiang
	Biopharmaceutics	Not assigned this review cycle	
	Microbiology	Not assigned this review cycle	
	Other (specify):	Not assigned this review cycle	
	RBPM	Omolara Oyinlola-Adeyemi	
	ATL	Molly Lee	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 204311 for the commercialization of Abacavir and Lamivudine Tablets for Oral Suspension 60 mg/30 mg packaged in 60-count bottles. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective.

NDA 204311 received tentative approval (TA) on October 23, 2014. The tentative approval action letter contained the following information:

> *This NDA was reviewed under the President's Emergency Plan for AIDS Relief (PEPFAR). Based on the data provided, the expiration dating period is 24 months for Abacavir and Lamivudine Tablets for*

Oral Suspension, 60 mg/30 mg in the following packaging configuration when stored below 30ºC (86ºF): 1) HDPE bottle packs of 60 tablets with cotton, screw caps, induction seals, and desiccant (silica gel), 2) HDPE bottle packs of 60 tablets with cotton, screw caps, and induction seals for commercial packaging, (b) (4) (b) (4)

On February 6, 2019, the Applicant resubmitted the NDA for final approval (NDA-204311-ORIG-1-RESUB-21). The NDA was issued Complete Response (CR) Letters on August 6, 2019 and January 13, 2023 due to unresolved concerns with the manufacturing facilities. The current resubmission responded to the CR letter dated January 13, 2023, including the compliance status change for DS facility for Abacavir, MLL Unit-8 (FEI 3002785310), previously OAI status, to NAI following a for-cause inspection in May 2023. (b) (4) (b) (4)

The Applicant previously provided adequate drug substance information either in the NDA or the respective DMFs (Abacavir Sulfate USP: DMF # (b) (4) Lamivudine USP: DMF #s (b) (4) and (b) (4) The Applicant provided adequate drug product and biopharmaceutics information to ensure the identity, purity, and strength to support the proposed commercial drug product. The overall manufacturing process and controls were not changed in this review cycle and were previously found to be adequate. All facilities are currently acceptable for the proposed functions. The proposed labeling and container labels have been reviewed, and sufficient product quality data was provided to support the administration instructions in the labeling. Recommendations and revisions have been communicated to OND (to be communicated to the Applicant) to ensure adequate information is included in the prescribing information to meet the regulatory requirements.

On December 6, 2023, the Applicant confirmed that (b) (4) (b) (4) (b) (4) The Applicant also confirmed that the 60-count bottle with a screw (non-child-resistant) closure will be used in PEPFAR countries, while the 60-count bottle with a child-resistant (CR) closure will be used for commercialization in the US. It was also indicated that a placeholder NDC number was used on the CR container/carton labels, as an official NDC number will be assigned should Mylan decide to commercialize the

product in the US in the future. There is adequate CMC information provided to support both the non-CR and CR bottles proposed for commercialization.

(b) (4)

The current proposal is to (b) (4) (b) (4) only list the CR packaging configuration in Section 16 of the Prescribing Information. At the time of writing this executive summary, OND Policy has been consulted to ensure this approach is acceptable, and this review will be updated if there are any changes.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments: N/A

Molly Lee

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	204311
Assessment Cycle Number	4
Drug Product Name	Abacavir and Lamivudine Tablets for Oral Suspension

Assessment Recommendation: Adequate *pending revisions conveyed to OND*

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	
Patient Information	Inadequate	
Instruction for Use (IFU)	Inadequate	
Container Labels	Inadequate	
Carton Labeling	Inadequate	

Brief Description of Outstanding Issues:

Revisions related to the product title and route of administration, salt equivalency statements, and storage conditions should be implemented in order to comply with current best labeling practices. After the recommended changes, the labeling will be adequate from the product quality perspective.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 0034, SDN 35	07/15/2023	Carton and Container Labeling Prescribing Information Warning Card Medication Guide Instructions for Use

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

Adequate pending revisions conveyed to OND.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Inadequate	Route of administration is in the product title, i.e., "ABACAVIR and LAMIVUDINE tablets for oral suspension". Stating (b) (4) (b) (4) " after the product title is unnecessary based on the FDA Product Title Guidance (FDA Product Title Guidance)
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	Placeholder present
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not " (b) (4) descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	Adequate	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

Assessment: *Inadequate*

(b) (4)

[redacted]

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	Inadequate	Revise to put suspension of tablets in water as the first method of administration as the product title is "abacavir and lamivudine tablets for oral suspension".
Important administration instructions supported by product quality information (e.g., do not	Adequate	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
crush or chew extended-release tablets, instructions for mixing with food).		
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Inadequate*

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

(b) (4)

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color,	Adequate	

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
coating, scoring, imprinting, and color and clarity of the solution, when applicable.		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	Adequate	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

(b) (4)

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	Remove unnecessary repetition

[15] Use of “USP” descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the “USP” descriptor next to the established name in

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Inadequate	Statement "(b) (4) (b) (4) (b) (4)" should be removed.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	

the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	Inadequate	Remove (b) (4). (b) (4) after abacavir sulfate and lamivudine should be removed for clarity and conciseness.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Inadequate*

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[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	Adequate	

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Inadequate	Missing statement "Dispense in the original container and keep the container tightly closed to protect from moisture", which is present on the carton and container labels.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	Revise from "Store below 30°C" to (b) (4) [redacted]
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	

Assessment: *Inadequate*

(b) (4)

1.2.5 Other Sections of Labeling

Section 17

(b) (4)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Medication Guide

(b) (4)

Instructions for Use

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	Inadequate	Images in IFU should be revised to more accurately depict the volume of water used for preparing the suspension.
Storage and handling information (if applicable).	Inadequate	Missing statement "Dispense in the original container and keep container tightly closed to protect from moisture" in both the Medication Guide and Instructions for Use. Temperature should be revised to "Store at 68°F to 77°F (20°C to 25°C)".
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of	Adequate	

[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
the desiccant differ from the dosage form.		
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Inadequate*

Medication Guide

(b) (4)

Instructions for Use

(b) (4)

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Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Inadequate	Yes	Salt equivalency statement is incomplete. Revise to "Each tablet contains 60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate)…"
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Inadequate	Yes	Missing on both the carton label and the container label.
Storage conditions. If applicable, include a space on the carton labeling for the	Inadequate	Yes	Revise from "Store below 30°C (86°F)" to (b) (4)

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
user to write the beyond-use-date (BUD).			(b) (4)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Choose an item.	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Choose an item.	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See	Adequate	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Prescribing Information" [§ 201.5 & 201.55].			
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Choose an item.	

[31] USP General Notices 3.20 Indicating Conformance

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
And others if space is available.	Inadequate	Yes	Remove (b) (4) for abacavir sulfate and lamivudine.

Assessment of Carton Labels and Container Labeling: *Inadequate*

1. Revise salt equivalency statement to "Each tablet contains 60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate)…"
2. Lot number and expiration date placeholders are missing on both the carton label and container label.
3. Revise the storage condition from "Store below 30°C (86°F)" to "Store at 20°C to 25°C (68°F to 77°F)".
4. Remove (b) (4) for abacavir sulfate and lamivudine.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Recommendations and revisions have been conveyed to OND. Labeling will be adequate from the product quality perspective once the changes have been implemented by the Applicant.

Primary Labeling Assessor Name and Date:
Hudson Roth, Ph.D., 11/07/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):
David Claffey, Ph.D., 11/07/2023

Hudson Roth

Digitally signed by Hudson Roth
Date: 11/14/2023 12:27:10PM
GUID: 6179adc200758f92383849fa56daa5d6

David Claffey

Digitally signed by David Claffey
Date: 11/14/2023 01:06:07PM
GUID: 508da71e00029e20b201195abff380c2

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NDA Executive Summary

1. Application/Product Information

NDA Number.	204311		
Applicant Name	Mylan Laboratories Limited		
Drug Product Name	Abacavir and Lamivudine Tablets for Oral Suspension (60 mg/30 mg)		
Dosage Form.	Tablet, for suspension		
Proposed Strength(s)	60 mg/30 mg (abacavir/lamivudine)		
Route of Administration	Oral		
Maximum Daily Dose	600 mg abacavir; 300 mg lamivudine		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of human immunodeficiency virus type 1 (HIV-1) infection in combination with other antiretroviral agents.		
Drug Product Description	White to off white, round, (b) (4) tablet debossed with AL above the score and 7 below the score on one side and M on the other side of the tablet containing the following actives: 60 mg of abacavir and 30 mg of lamivudine		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store below 30ºC (86°F)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kanny Wan	Katherine Windsor
	Drug Product/ Labeling	Hudson Roth	Pete Guerrieri
	Manufacturing	Chunsheng Cai	Bo Jiang

	Biopharmaceutics	Haridikkum Patel	Elsbeth Chikhale
	Microbiology	N/A	
	Other (specify):		
	RBPM	Erica Keafer	
	ATL	Pete Guerrieri	

2. Final Overall Recommendation - Complete Response

3. Deficiencies

Following surveillance inspection of the Mylan Laboratories Limited Unit-8 (FEI 3002785310, Vizianagaram, Andhra Pradesh, India) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this NDA may be approved.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg are indicated for treatment of HIV. The product is a fixed dose combination tablet for oral suspension. The tablets are white to off white, round, (b) (4) (b) (4) tablets debossed with AL above the score and 7 below the score on one side and M on the other side of the tablet.

This application received Tentative Approval on October 23, 2014. Patent expiration now allows marketing in the US, and the applicant submitted an amendment on 02/06/2019 for final approval. The NDA was CR'd on 08/06/2019 for facility deficiencies at Mylan Laboratories Limited, Unit 8 (FEI 3002785310) due to observations made during an inspection of the abacavir sulfate drug substance manufacturing site in late May 2019. This facility remains out of compliance in this review, and therefore the submission is recommended as withhold from a manufacturing view, and the submission will be recommended for CR.

In this resubmission, the applicant proposed an additional drug substance manufacturer ((b) (4)) and manufacturing process for Lamivudine drug substance. The batch data for drug substance batches used to manufacture the new drug product exhibit batch and the drug substance specifications used for retest by the drug product manufacturers were provided in the resubmission and found adequate.

One additional batch of the drug product was manufactured in support of the above changes using Abacavir Sulfate drug substance from Mylan Laboratories Limited, Unit-10 and Lamivudine drug substance from (b) (4) (b) (4), and the drug substance batches were found adequate for use. Twelve months long-term and six months accelerated stability data were provided for the new drug product batch. Comparative dissolution data between drug product batches manufactured with APIs pre-change and post-change using the QC dissolution method were submitted and found adequate. The supportive data for the new batch are appropriate to support the drug substance updates. However, the overall submission recommendation is CR due to the facility status described above.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Inadequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comparability Protocols (PACMP): No

Additional Lifecycle Comments: N/A

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 12/19/2022 10:34:49AM
GUID: 54eb8ba100062ea99cbaab7c64143df3

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 204311
Assessment #3

Drug Product Name	Abacavir and Lamivudine Tablets for Oral Suspension (60 mg/30 mg)
Dosage Form	Tablet, for suspension
Strength	60 mg/30 mg (abacavir/lamivudine)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Mylan Laboratories Limited
US agent, if applicable	Mylan Pharmaceuticals Inc., a Viatris Company 3711 Collins Ferry Road Morgantown, WV 26505 Attn: Beth Britton, Sr. Director, Regulatory Affairs Email: beth.britton@viatris.com

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD SN 0034	07/15/2022	All
eCTD SN 0034	08/18/2022	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Kanny Wan	Katherine Windsor
Drug Product	Hudson Roth	Pete Guerrieri
Manufacturing	Chunsheng Cai	Bo Jiang

Microbiology	N/A	
Biopharmaceutics	Haridikkum Patel	Elsbeth Chikhale
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Pete Guerrieri	
Environmental	N/A	

QUALITY ASSESSMENT DATA SHEET

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	Mylan Labs Ltd.	Abacavir Sulfate USP	Adeq.	See DS review	
	II	Mylan Labs Ltd.	Lamivudine USP	Adeq.	See DS review	
	II	Mylan Labs Ltd.	Lamivudine USP	Adeq.	See DS review	
	III & IV				See DP review	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 204311 is recommended for Complete Response from the product quality perspective, due to unresolved concerns with the manufacturing facility, Mylan Laboratories Limited, Unit 8 (FEI 3002785310).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg are indicated for treatment of HIV. The product is a fixed dose combination tablet for oral suspension. The tablets are white to off white, round, (b) (4) (b) (4) debossed with AL above the score and 7 below the score on one side and M on the other side of the tablet.

This application received Tentative Approval on October 23, 2014. Patent expiration now allows marketing in the US, and the applicant submitted an amendment on 02/06/2019 for final approval. The NDA was CR'd on 08/06/2019 for facility deficiencies at Mylan Laboratories Limited, Unit 8 (FEI 3002785310) due to observations made during an inspection of the abacavir sulfate drug substance manufacturing site in late May 2019. This facility remains out of compliance in this review, and therefore the submission is recommended as withhold from a manufacturing view, and the submission will be recommended for CR.

In this resubmission, the applicant proposed an additional drug substance manufacturer ([(b) (4)]) and manufacturing process for Lamivudine drug substance. The batch data for drug substance batches used to manufacture the new drug product exhibit batch and the drug substance specifications used for retest by the drug product manufacturers were provided in the resubmission and found adequate.

One additional batch of the drug product was manufactured in support of the above changes using Abacavir Sulfate drug substance from Mylan Laboratories Limited, Unit-10 and Lamivudine drug substance from [(b) (4)], and the drug substance batches were found adequate for use. Twelve months long-term and six months accelerated stability data were provided for the new drug product batch. Comparative dissolution data between drug product batches manufactured with APIs pre-change and post-change using the QC dissolution method were submitted and found adequate. The supportive data for the new batch are appropriate to support the drug substance updates.

Proposed Indication(s) including Intended Patient Population	Treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric patients aged 3 months and older or weighing at least 5 kg, in combination with other antiretroviral agents.
Duration of Treatment	Chronic
Maximum Daily Dose	600 mg abacavir; 300 mg lamivudine
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The NDA was recommended for approval from the drug substance perspective at the conclusion of the previous assessment cycle. In the previous NDA submissions, the applicant cross-referenced the CMC information for Abacavir Sulfate drug substance to DMF [(b) (4)] and that for Lamivudine drug substance to DMF [(b) (4)] The content of both DMFs remains adequate to support this NDA.

In this resubmission, the applicant proposed an additional drug substance manufacturer ([(b) (4)]) and manufacturing process for lamivudine drug substance, and cross-referenced the CMC information to DMF [(b) (4)] The Lamivudine drug substance information in DMF [(b) (4)] is adequate to support this NDA.

The applicant notes the following additional drug substance-related updates in the resubmission since the previous NDA assessment: (1) inclusion of an additional new manufacturing site, Mylan Laboratories Limited, Unit 10, (b) (4) for Abacavir Sulfate drug substance, and (2) drug substance updates for Lamivudine drug substance. These updates have been assessed under the reviews of DMFs (b) (4) and (b) (4) In this resubmission, in support of all proposed changes, one additional batch of the drug product was manufactured using abacavir sulfate drug substance from Mylan Laboratories Limited, Unit-10 and lamivudine drug substance from (b) (4). The batch data for drug substance batches used to manufacture the new drug product exhibit batch and the drug substance specifications used for retest by the drug product manufacturers were provided in the resubmission and found adequate. Stability data in the respective referenced DMFs support the drug product manufacturers' proposed retest periods for both drug substances: (b) (4) (b) (4)

The NDA is recommended for approval from the drug substance perspective. For additional information, see Dr. Kanny Wan's review below.

Drug Product: Adequate

The previous submission was reviewed and found adequate from the drug product quality perspective by David Amspacher, Ph.D. in June 2019 during review cycle #2. As such, no outstanding drug product issues from the previous review cycle needed to be addressed by the Applicant in this resubmission.

The following information was provided for a drug product batch manufactured with the drug substances sourced from the new manufacturing sites, as described in the drug substance section above:

a) certificate of analysis
b) residual solvent analysis (for both drug substances)
c) elemental report
d) stability data - six months of accelerated (40°C/75% RH), 12 months of long-term (30°C/75% RH) and 90 days of in-use (30°C/75% RH)

The applicant also proposed (b) (4) (b) (4) (b) (4). Sufficient data to support the safety and quality of the drug product with the above changes were provided.

This application is recommended for approval from the drug product quality perspective. For additional information, see Dr. Hudson Roth's review below.

Labeling: Adequate

Labeling recommendations will be conveyed to OND. For additional information, see Dr. Hudson Roth's review below.

Manufacturing: Inadequate

The current resubmission responded to the CR letter dated 8/6/2019, providing drug substance process updates for the existing lamivudine, USP DMF (b) (4) and adding an alternate new drug substance abacavir facility, Mylan Lab Unit-10 under the existing DMF (b) (4) and a new supplier for lamivudine with two manufacturing sites, (b) (4) (b) (4) and Mylan Unit 1/Unit2, under a new DMF (b) (4)

The current NDA resubmission includes one new (b) (4) facility submitted in DMF (b) (4) and seven new facilities submitted with the DMF (b) (4) (b) (4) Additional details for these facilities and their assessments are provided in the manufacturing review below. In conclusion of the current assessment, all new facilities are acceptable. However, the original Abacavir facility, Mylan Lab Unit 8, (FEI 3002785310 is still out of compliance, and the final facility assessment remains inadequate.

In the resubmission, the firm also included a scale up proposal for the DP manufacturing process. The exhibit batch scale was (b) (4) kg, and proposed commercial batch size is (b) (4) kg, which is the same as the previously approved commercial batch size. New exhibit batch data are provided using the proposed new supplier for Abacavir and new supplier for Lamivudine; no changes are noted in the manufacturing process control. All in-process testing results comply with the proposed in-process specifications. The process remains adequate; however, the overall recommendation is inadequate as a result of the withhold recommendation for the Mylan Lab Unit 8 facility.

For additional information, see Dr. Chunsheng Cai's review below.

Biopharmaceutics: Adequate

This Biopharmaceutics Review evaluates the comparative dissolution profiles between drug product batches manufactured with APIs pre-change and post-change to support the proposed addition of a new DMF (b) (4) for lamivudine and addition of a new alternate drug substance manufacturing site with (b) (4) for abacavir sulfate.

The applicant's proposed dissolution method (900 mL of 0.1 N HCl, Paddle, 75 RPM) and acceptance criteria (Abacavir: Q= (b) (4)% at 15 min Lamivudine: Q= (b) (4)% at 15 min) were found adequate in the previous Biopharmaceutics assessment. Both APIs are highly soluble drug substances as per BCS criteria. Therefore, the risk is low from a Biopharmaceutics perspective. (b) (4) which was found acceptable during the previous Biopharmaceutics assessment. The applicant has submitted comparative dissolution data between drug product batches manufactured with APIs pre-change and post-change using the QC dissolution method.

The drug product exhibits very rapid in-vitro dissolution, that is, more than (b) (4)% of the drug (each API) is dissolved within 15 minutes for both the pre-change and the post-change batches. The provided comparative dissolution data support the proposed changes for each API. In addition, the applicant has provided 12 months long term and 6 months accelerated stability data for new drug product batch # 2020492. The provided dissolution data for the stability studies are adequate.

From a Biopharmaceutics perspective, the NDA is adequate and recommended for approval. For additional information, see Dr. Hardikkumar H. Patel's review below.

Microbiology: N/A

C. Risk Assessment

See Review #1

D. List of Deficiencies for Complete Response

1. Manufacturing Deficiencies

Following surveillance inspection of the Mylan Laboratories Limited Unit-8 (FEI 3002785310, Vizianagaram, Andhra Pradesh, India) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this NDA may be approved.

Application Technical Lead Name and Date:

Pete Guerrieri, PhD

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

NDA 204311

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:
Recommend changes to Highlights and Section 11 for clarity and consistency throughout the PI.
Special handling instructions should be included in Section 16 and the Medication Guide.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	The (b) (4) portion of the drug product title can be removed. **Original:** (b) (4) " **Revised:** "ABACAVIR and LAMIVUDINE tablets for oral suspension"
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

package and imaging bulk package.		
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Directions for preparing the suspension are provided
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Statements to not chew tablets (b) (4) (b) (4) are included in the administration instructions.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever*	N/A	

solution and container permit"		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Remove (b) (4) for consistency throughout the PI. **Current:** (b) (4) **Revised:** "…60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate) and 30 mg of lamivudine…"
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Adequate	
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state “DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]” with x numerical citation to “OSHA Hazardous Drugs.”	Inadequate	Carton and container labels have the statement “Dispense in original container” (b) (4) [redacted]
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Statement “Store below 30 °C (86 °F)” is acceptable for PEPFAR product.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *“Not made with natural rubber latex. Avoid statements such as “latex-free.”*	N/A	
Include information about child-resistant packaging	Adequate	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Inadequate	Carton and container labels have the statement "Dispense in original container" (b) (4) [redacted]
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

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[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Inadequate	Equivalency statement is incomplete. **Current:** (b) (4) [redacted] **Revised:** "Each tablet contains 60 mg of abacavir as 70.2 mg of abacavir sulfate"
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Inadequate	Not included on either the carton or container labels.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Inadequate*

Salt equivalency statement is incomplete, and the lot number and expiration date locations are not indicated.

ITEMS FOR ADDITIONAL ASSESSMENT

Comments on the Prescribing Information and Medication Guide:

1. We recommend removing the (b) (4) portion of the product title in the highlights of the prescribing information (i.e., "ABACAVIR and LAMIVUDINE tablets for oral suspension")
2. We Recommend removing "(b) (4)" after the drug substance names in Section 11 (i.e., revise "(b) (4)" to "abacavir sulfate" and "(b) (4) (b) (4)" to "lamivudine") to maintain consistency throughout the PI.
3. The carton and container labels contain the statement "Dispense in original container". (b) (4) (b) (4)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Comments on the Container and Carton Labeling:

1. The salt equivalency statement is incomplete as the amount of abacavir sulfate is not indicated. Revise to “Each tablet contains 60 mg of abacavir as 70.2 mg of abacavir sulfate”.
2. The carton and container labels should have a location designated for where the lot number and expiration date will be printed.

Overall Assessment and Recommendation:

The PI will be adequate once the recommendations are considered by the Applicant and the inclusion of special handling directions is added to Section 16 and the Medication Guide.

The carton and container labeling will be adequate once the salt equivalency statement is corrected and there is a designated location for the lot number and expiration date.

Recommended edits to be conveyed to OND.

Primary Labeling Assessor Name and Date:
Hudson Roth, Ph.D. 12/06/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Peter Guerrieri, Ph.D. 12/06/2022

Hudson Roth

Digitally signed by Hudson Roth
Date: 12/07/2022 09:13:39AM
GUID: 6179adc200758f92383849fa56daa5d6

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 12/15/2022 05:18:04PM
GUID: 54eb8ba100062ea99cbaab7c64143df3

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BIOPHARMACEUTICS REVIEW	
Application No.	NDA-204311-ORIG-1-RESUB-35
Applicant	Mylan Labs Limited
Product Name/ Strength(s)	Abacavir Sulfate and Lamivudine Tablets for Oral Suspension (EQ 60 mg/30 mg)
Dosage Form/Route of Administration	Tablets for Oral Suspension
Indication	Treatment of HIV type l (HIV-1) infection in pediatric patients aged 3 months and older or weighing at least 5 kg
Submission Date(s)	07/15/2022
Listed drugs (LDs)	ZIAGEN® (abacavir sulfate) Oral Solution EQ 20 mg/mL (NDA 020978) EPIVIR® (lamivudine) Oral Solution, 10 mg/mL (NDA 020596)
Primary Reviewer	Hardikkumar H. Patel, Ph.D.
Secondary Reviewer	Elsbeth G. Chikhale, Ph.D.
Recommendation	**Adequate**

EXECUTIVE SUMMARY

The Applicant is seeking approval for Abacavir Sulfate and Lamivudine Tablets for Oral Suspension EQ 60 mg/30 mg for the treatment of HIV-1 infection in pediatric patients (aged 3 months and older or weighing at least 5 kg) via the 505(b)(2) regulatory pathway. The listed drugs (LDs) are ZIAGEN® (abacavir sulfate) Oral Solution EQ 20 mg/mL (NDA 020978) and EPIVIR® (lamivudine) Oral Solution, 10 mg/mL (NDA 020596). The proposed drug product is bridged to the listed drugs via in-vivo BE studies. This NDA is being submitted under the provisions of PEPFAR.

This application was Tentatively Approved (TA) on 10/23/2014. Request for final approval was received on 2/6/2019. However, TA status was changed on 8/6/2019 to Complete Response (CR) due to facility issues (at Mylan Laboratories Limited, Unit 8, FEI # 3002785310) and labeling deficiencies. The Applicant has submitted a response to the CR letter in this amendment (NDA-204311-ORIG-1-RESUB-35). The response also includes 1) addition of a new DMF (b) (4) for lamivudine and 2) addition of a new alternate drug substance manufacturing site with an (b) (4) for abacavir sulfate (in existing DMF (b) (4).

This Biopharmaceutics Review evaluates the comparative dissolution profiles between drug product batches manufactured with APIs before and after the proposed API changes to support the proposed addition of a new DMF (b) (4) for lamivudine and addition of a new alternate drug substance manufacturing site with (b) (4) for abacavir sulfate.

Previously tentative approved Dissolution Method and Acceptance Criteria:

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criteria
II (Paddle)	75 RPM	0.1 N HCl	900 mL/ 37.0 ± 0.5 °C	Abacavir: Q= (b) (4) % at 15 min Lamivudine: Q= (b) (4) % at 15 min

Dissolution Data:

The comparative dissolution data submitted supports the proposed new DMF for lamivudine and addition of a new alternate drug substance manufacturing site for abacavir sulfate.

Recommendation:

The Biopharmaceutics recommendation for NDA-204311-ORIG-1-RESUB-35 for Abacavir Sulfate and Lamivudine Tablets for Oral Suspension EQ 60 mg/30 mg is **adequate** and recommended for **Approval**.

BACKGROUND

The FDA Tentatively Approved (TA) NDA 204311 on 10/23/2014. However, TA status was changed to Complete Response (CR) due to facility issues and labeling deficiencies on 8/6/2019.

The Applicant has submitted a response to the CR letter in this amendment (NDA-204311-ORIG-1-RESUB-35). The response also proposes changes for both APIs as follow:

1) Insignificant changes to lamivudine (existing DMF (b) (4))
2) Addition of **new DMF** for lamivudine (DMF (b) (4)). The new DMF included two drug substance manufacturing sites with an identical manufacturing process.
3) Addition of a new alternate drug substance manufacturing site with (b) (4) for abacavir sulfate (**in existing DMF** (b) (4)

The Applicant has submitted comparative dissolution data between drug product batches manufactured with APIs before change and after change using the QC dissolution method (900 mL of 0.1 N HCl, Paddle, 75 RPM) to support the proposed addition of a new DMF (b) (4) for lamivudine and addition of a new alternate drug substance manufacturing site with (b) (4) for abacavir sulfate.

REVIEW'S OBJECTIVE

This Biopharmaceutics Review evaluates the comparative dissolution profiles between drug product batches manufactured with APIs pre-change and post-change to support the proposed addition of a new DMF (b) (4) for lamivudine and addition of a new alternate drug substance manufacturing site with (b) (4) for abacavir sulfate.

BIOPHARMACEUTICS ASSESSMENT

The Applicant's proposed dissolution method (900 mL of 0.1 N HCl, Paddle, 75 RPM) and acceptance criteria (Abacavir: Q= (b) (4)% at 15 min Lamivudine: Q= (b) (4)% at 15 min) were found adequate in the previous Biopharmaceutics assessment. Both APIs are highly soluble drug substances as per BCS criteria. Therefore, the risk is low from a Biopharmaceutics perspective. It appears that the two APIs are (b) (4), which was found acceptable during the previous Biopharmaceutics assessment. The Applicant has submitted comparative dissolution data between drug product batches manufactured with APIs pre-change and post-change using the QC dissolution method as follow:

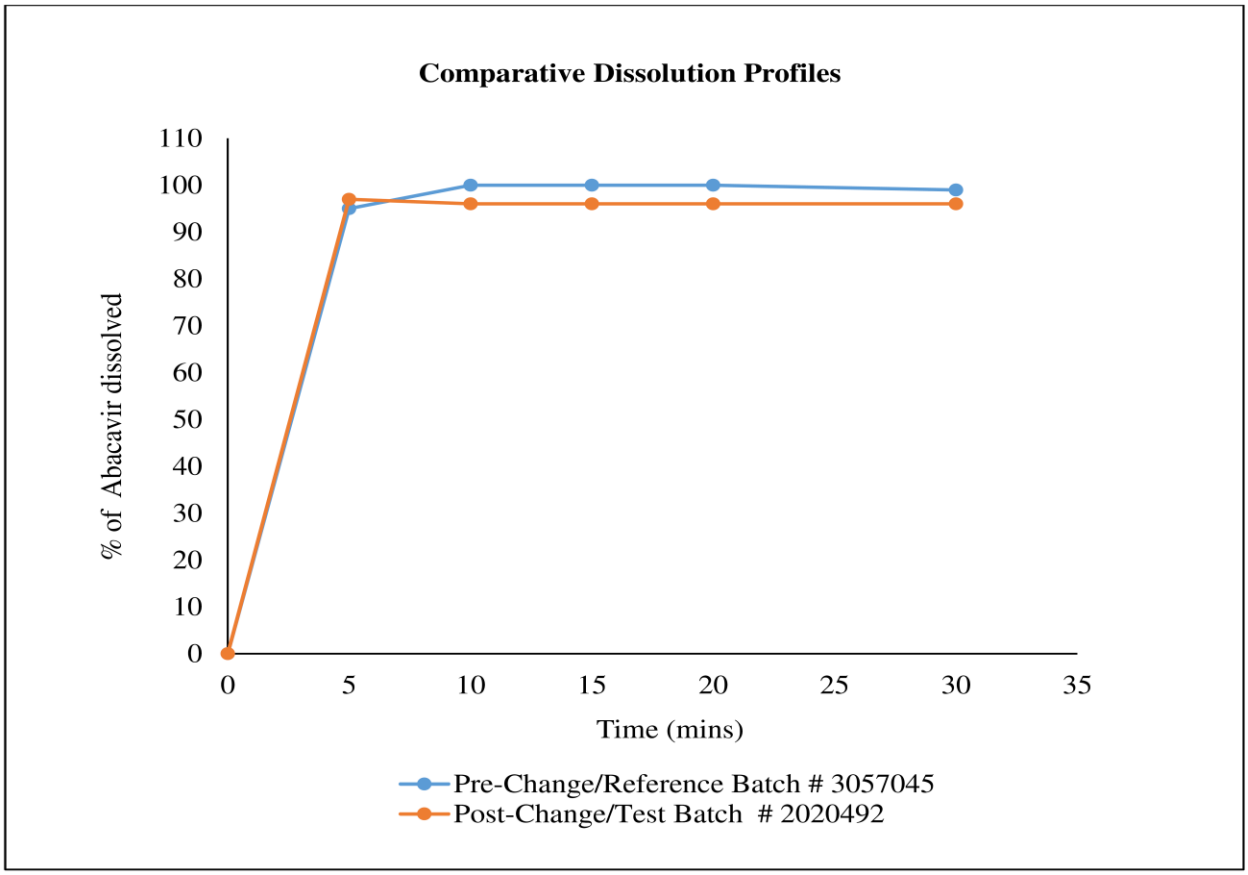

Figure 1: Comparative dissolution profiles of Abacavir using the QC dissolution method (900 mL 0.1 N HCl, Paddle, 75 RPM)

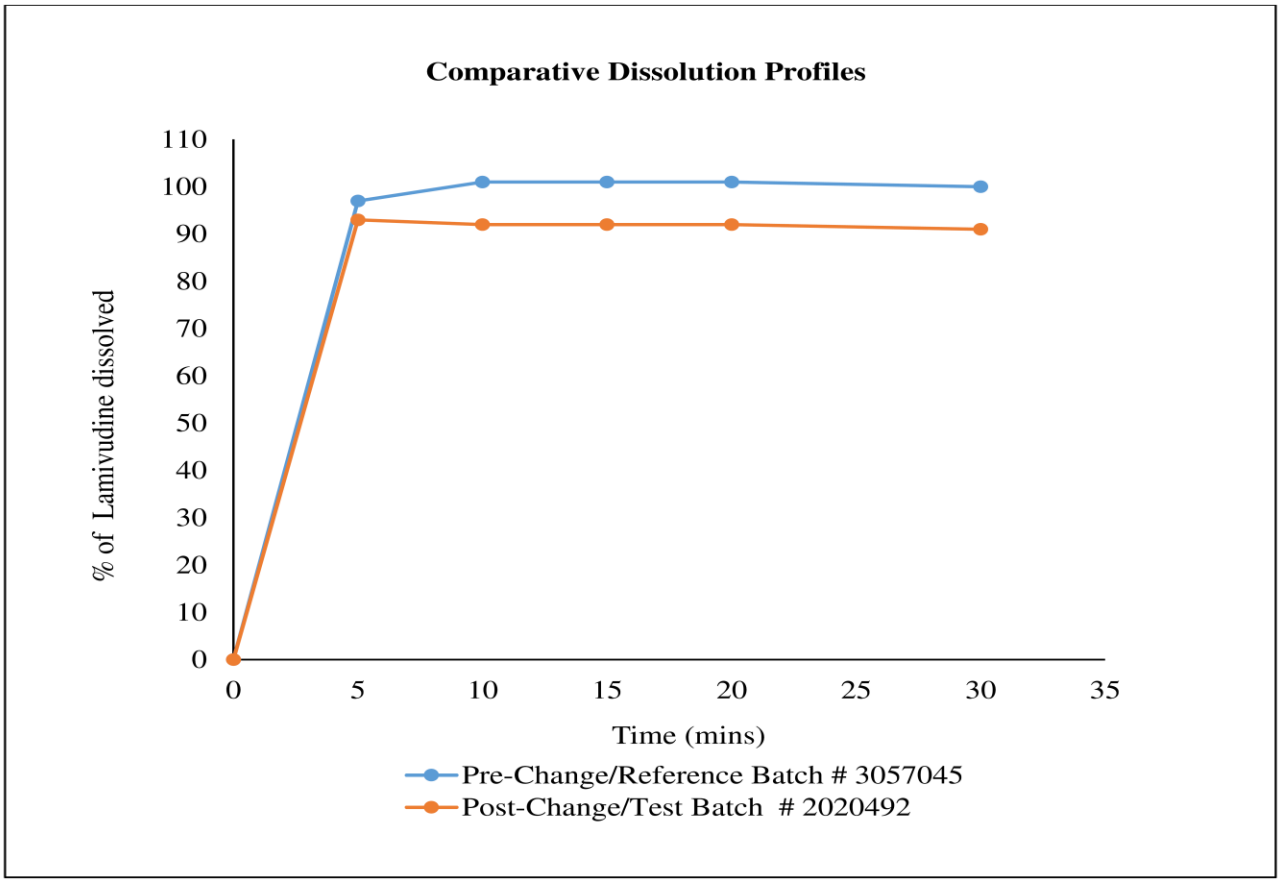

Figure 2: Comparative dissolution profiles of Lamivudine using the QC dissolution method (900 mL 0.1 N HCL, Paddle, 75 RPM)

The drug product exhibits very rapid in-vitro dissolution, that is, more than (b) (4)% of the drug (each API) is dissolved within 15 minutes for both the pre-change and the post-change batches. The provided comparative dissolution data support the proposed changes for each API. In addition, the Applicant has provided 12 months long term and 6 months accelerated stability data for new drug product batch # 2020492. The provided dissolution data for the stability studies are adequate.

RECOMMENDATION

From a Biopharmaceutics perspective, NDA-204311-ORIG-1-RESUB-35 for Abacavir Sulfate and Lamivudine Tablets for Oral Suspension EQ 60 mg/30 mg is **adequate** and recommended for **Approval**.

Hardikkumar Patel

Digitally signed by Hardikkumar Patel
Date: 11/29/2022 10:53:51AM
GUID: 5435662600016f7b78898063ba9a457e2

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 11/29/2022 10:59:03AM
GUID: 50743ccc000031928b54eba1769a5df9

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER P GUERRIERI
12/19/2022 11:11:05 AM

OPQ Combined Review for NDA 204311 Orig-1 Resub-21

Product: Abacavir and Lamivudine Tablets for Oral Suspension, 60mg/30mg
Applicant: Mylan
Submitted: Feb 6, 2019
Review #1: July 1, 2019
PDUFA: Aug 6, 2019

This amendment is recommended for COMPLETE RESPONSE from the product quality perspective at this time.

Summary:
This application received Tentative Approval on October 23, 2014. Patent expiration now allows marketing in the US, and the applicant submitted this amendment for final approval. There have been 8 Post-TA amendments reviewed and approved since 2014, and Mylan has submitted 4 annual reports during this time. Because of observations made during an inspection of the abacavir sulfate drug substance manufacturing site (FEI 3002785310) in late May, 2019, this amendment cannot be recommended for approval at this time. A complete evaluation of the inspectional results and the firm's responses will be completed prior to the PDUFA goal date, at which time the OPQ recommendation for this amendment will be reevaluated. A second OPQ review will document that recommendation.

Facilities:

- Because of observations made during the May-June 2019 inspection of the Mylan Unit-8 site (FEI 3002785310), this facility is currently listed in Panorama as potential Official Action Indicated (pOAI) with a recommendation to Withhold Approval of this amendment. This facility manufactures abacavir sulfate drug substance.

Once the evaluation of the inspectional results and the firm's responses has been completed, the OPQ recommendation for this amendment will be reevaluated.

Based on evaluation of inspectional histories and responsibilities, the following facilities are acceptable at this time:

- Mylan-Indore (FEI 3010453141) DP manufacturing
- Mylan-Nashik (FEI 3005587313) DP manufacturing
- Mylan Unit-1/Unit-2 (FEI 3004713397) Lamivudine DS manufacturing
- Mylan-Aurangabad (FEI 3008316970) testing of packaging components

For additional details, see Dr. Chunsheng Cai's evaluations, as documented in Panorama's Facility View, and Facility Submission Status View.

Deficiency Comment for Action Letter: If needed after complete evaluation of the facility, the deficiency comment will be included in the next OPQ review for this amendment.

Drug Substance:
The drug substance information for this NDA is referenced to two Drug Master Files:

- DMF (b) (4) – Abacavir sulfate; Mylan is the holder. This DMF was recently reviewed (D. Yu; 13-Nov-2018) – through the amendment dated 09-Nov-2018 (SD58). No subsequent amendments have been received. The DMF remains adequate.
- DMF (b) (4) – Lamivudine; Mylan is the holder. This DMF was recently reviewed (Q. Shi; 19-Nov-2018) – through the amendment dated 27-Nov-2018 (SD87). No subsequent amendments have been received. The DMF remains adequate.

For additional details regarding the two drug substances, see Dr. Monica Cooper's drug substance review, below.

Drug Product:
The packaging for commercial distribution in the US will be HDPE bottles of 60 tablets with induction seals and child-resistant caps. A certification that the container-closure system conforms to the Consumer Product Safety Commission regulations was provided. The bottles and caps can be (b) (4) in the commercial packaging. An equivalency report in the April 9, 2019 amendment adequately links the existing stability data collected in bottles with screw-caps with the proposed commercial packaging. The proposed 24-month expiration dating period is supported by the stability data under 30°C/75%RH conditions (22 months for tablets made at the Indore facility; up to 24 months for tablets made at the Nashik facility). The applicant confirmed in the April 9, 2019 amendment that final approval is being requested for tablets made at either the Indore or Nashik manufacturing facilities. (b) (4) (b) (4) and all attributes remain well within the acceptance criteria. The product is recommended for storage below 30° (86°).

Upon request, a consolidated drug product specification table was submitted, showing acceptance criteria at both release and shelf-life. An adequate risk assessment for elemental impurities was submitted on December 13, 2018, following ICH Q3D Option-2b approach. No additional controls are necessary, because the quality system and process controls are sufficient. Data supporting the dispersion of the tablet in water, and supporting the quality of the half-tablets, were found to be adequate in the September 15, 2014 CMC review.

For additional details regarding the drug product, including a summary of information and changes that were submitted, reviewed, and permitted since the original Tentative Approval, see Dr. David Amspacher's drug product review, below.

Labeling:
Edits recommended from the product quality perspective for the prescribing information and the container labels will be conveyed to the OND review team, for consideration during labeling negotiations. See Dr. Amspacher's labeling review, below, for additional details.

Biopharmaceutics:
No reevaluation was needed for this amendment.

Process:
No reevaluation was needed for this amendment.

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The sponser has provided adequate information on all product quality related aspects of the drug substance.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Abacavir (b) (4) (b) (4) (b) (4) Lamivudine (b) (4) (b) (4)	Adequate
Established name(s)	ABACAVIR AND LAMIVUDINE TABLETS FOR ORAL SUSPENSION	Adequate
Route(s) of administration	for oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets for Oral Suspension: 60 mg of abacavir and 30 mg of lamivudine	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	functionally scored	Adequate Tablet meets guidelines and criteria for a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	for oral use	Adequate Not for injection or parental administration

FULL PRESCRIBING INFORMATION

Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Method of Preparation: For children unable to swallow tablets, dispersion can be prepared by dispersing the required number of tablets in water using the following procedure: 1. Place the tablet(s) for oral suspension in a container and add two teaspoons (10 mL) of drinking water per tablet. 2. Swirl the container until the tablet(s) for oral suspension breaks up into pieces small enough for the child to swallow. A spoon can be used to crush the pieces, if needed. 3. Drink the mixture within 1 hour. 4. Rinse the container with an additional small amount of water and drink the contents to ensure that the entire dosage is taken. (b) (4) [redacted]	Adequate Instructions for product preparation including diluents and conditions for the stability of the reconstituted product are adequate

1.2.1 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets for Oral Suspension	Adequate
Strength(s) in metric system	60 mg of abacavir as abacavir sulfate, (b) (4) and 30 mg of lamivudine, (b) (4)	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Each tablet contains60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate (b) (4)) and 30 mg of lamivudine, (b) (4)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The 60 mg/30 mg tablets are white to off-white, round, scored tablets debossed with AL above the score and 7 below the score on one side of the tablet and M on the other side. (b) (4) (b) (4)	Adequate The sponsor gives and adequate description of the identifying characteristics of the dosage forms
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	functionally scored	Adequate Product meets guidelines and criteria for a scored tablet
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-	N/A	Not for injection

patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

1.2.2 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Abacavir and lamivudine tablets for oral suspension contain the following 2 synthetic nucleoside analogues: abacavir (ZIAGEN, also a component of TRIZIVIR®) and lamivudine (also known as EPIVIR or 3TC) with inhibitory activity against HIV-1	Adequate
Dosage form(s) and route(s) of administration	Abacavir and lamivudine tablets for oral suspension are for oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each tablet contains60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate (b) (4) and 30 mg of lamivudine, (b) (4)	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	crospovidone, microcrystalline cellulose, sodium stearyl fumarate, strawberry cream flavor permaseal (maltodextrin, modified starch, natural identical flavoring substance, natural flavoring substance and propylene glycol) and sucralose	Adequate All inactive ingredients provided
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic,	N/A	Not for injection

include the name and statement of effect.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	No alcohol present
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	inhibitory activity against HIV-1	Adequate
Chemical name, structural formula, molecular weight	chemical name of abacavir sulfate is (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol hemi sulfate. It has a molecular formula of (C14H18N6O)2•H2SO4 and a molecular weight of 670.76 g per mol. The chemical name of lamivudine is (-)-1-[(2R,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. It has a molecular formula of C8H11N3O3S and a molecular weight of 229.26 g per mol.	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	No chemical or physical properties applicable for administration

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No misleading statements	Adequate

1.2.1 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets for Oral Suspension	Adequate
Strength(s) in metric system	60 mg of abacavir as abacavir sulfate, (b) (4) and 30 mg of lamivudine, (b) (4)	Adequate
Available units (e.g., bottles of 100 tablets)	NDC (b) (4) carton of one bottle containing 60 tablets with induction seal and child-resistant cap	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The 60 mg/30 mg tablets are white to off-white, round, scored tablets debossed with AL above the score and 7 below the score on one side of the tablet and M on the other side	Adequate Sponsor provides shape, color, coating, scoring, and imprinting
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	functionally scored	Adequate Meets guidelines and criteria for a scored tablet
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Not for injection

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Dispense in original container with attached prescribing information that contains the Medication Guide and Warning Card.	Adequate Dispense in original container because of Medication Guide and Warning Card
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	No desiccant
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store below 30°C (86°F).	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	No latex
Include information about child-resistant packaging	child-resistant cap	Adequate

1.2.1 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

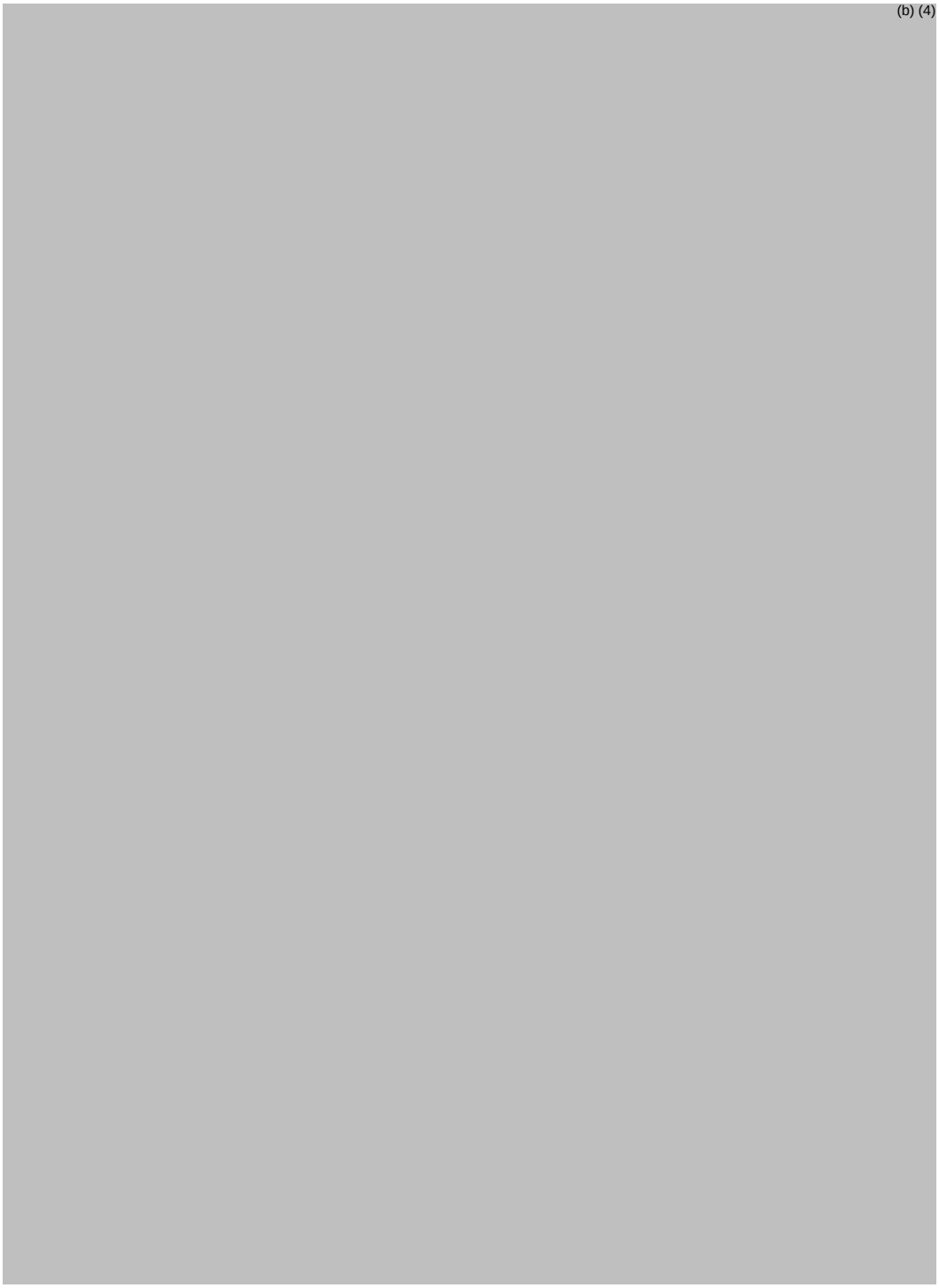
Please include your comments about other sections of labeling if they contain product quality information.

1.2.2 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Mylan Laboratories Limited Hyderabad — 500 096, India	Adequate

2.0 PATIENT LABELING

(b) (4)



Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

Quality-related items in the PI comply with regulatory requirements and are consistent with guidance recommendations, and CDER labeling policies. Product meets guidelines and criteria for a scored tablet. Dosage forms,

strengths, and identifying characteristics of the dosage forms are provided. USAN name and the dosage form are identical to an official USP monograph. Important administration instructions are provided and supported by product quality information in Module 3. Directions for dilution and preparation, strength (concentration) of the prepared solution to be administered, and storage conditions of the prepared solution are provided. Patient Labeling complies with all statutory/regulatory requirements and is consistent with guidance recommendations from a product quality perspective. This application is recommended for approval per labeling/labels perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Abacavir and Lamivudine Tablets for Oral Suspension	Adequate
Dosage strength	60 mg*/30 mg	Adequate
Route of administration	Oral Suspension	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate (b) (4) and 30 mg of lamivudine, (b) (4)	Adequate
Net contents (e.g. tablet count)	60 Tablets	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	(b) (4)	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store below 30°C (86°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	Not for injection
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	No alcohol
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Mylan Laboratories Limited Hyderabad — 500 096, India	Adequate
Medication Guide (if applicable)	(b) (4)	Adequate
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	Same as USP
And others, if space is available		

Assessment of Carton and Container Labeling: *{Adequate}*

The sponsor provides adequate carton and container labeling.

• Established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))
• Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))
• Route of Administration (21 CFR 201.100(b)(3))
• Net contents (21 CFR 201.51(a)) *
• Lot number per 21 CFR 201.18
• Expiration date per 21 CFR 201.17
• Name of all inactive ingredients (21 CFR 201.100(2)(b)(5). [201.10(a), 21CFR201.100(b)(5)(iii)]
• "Rx only" statement per 21 CFR 201.100(b)(1)
• Storage Conditions.
• NDC number per 21 CFR 201.2
• Bar Code per 21 CFR 201.25(c)(2)
• Name of manufacturer/distributor

• “See prescribing information for dosage information” (21 CFR 201.55)
• “Keep out of reach of children” (optional for Rx, required for OTC)

Overall Assessment and Recommendation: Adequate

The sponsor complies with all labeling requirements.

Primary Labeling Assessor Name and Date: David Amspacher 06/19/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): Balajee Shanmugam

David Amspacher

Digitally signed by David Amspacher
Date: 6/20/2019 07:41:19AM
GUID: 545aa993000701e1c86b8f251978551c

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 6/19/2019 04:33:13PM
GUID: 50758d5000003c1b1962e036ea11002c

BIOPHARMACEUTICS REVIEW Addendum Review (#2) Office of New Drug Quality Assessment			
Application No.:	NDA 204311	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	23 December 2013		
Division:	Division of Antiviral Products	**Team Lead:** Angelica Dorantes, Ph.D. **Supervisor (Acting)**: Paul Seo, Ph.D.	
Sponsor:	Mylan Laboratories, Ltd.	**Secondary Reviewer:** same as above	
Trade Name:	TBD	**Date Assigned:**	7 January 2014
		Primary Goal: **PDUFA Date:**	15 Sept 2014 23 Oct 2014
Generic Name:	Abacavir Sulfate and Lamivudine Scored Tablets for Oral Suspension (60/30 mg)	**Date of Review:**	14 October 2014 (Review #2)
Indication:	HIV-1 infection	**Type of Submission:** **505(b)(2),** PEPFAR	
Dosage/strengths	Tablet for oral suspension		
Route of Administration	Oral		

EXECUTIVE SUMMARY

NDA 204311 is submitted under section 505(b)(2) of the Food Drug & Cosmetics Act for the use of a functionally scored abacavir sulfate/lamivudine (60/30 mg) fixed dose combination (FDC) tablet to treat pediatric HIV patients.

Reference is made to the Biopharm-Quality Review dated 11 September 2014 (Review #1) for full details regarding the biopharmaceutics information submitted to NDA 204311. Biopharmaceutics Review #1 was finalized in DARRTS with a final approval recommendation pending completion of bioequivalence study site inspections. This review addendum includes the pivotal bioequivalence inspection report findings and Biopharmaceutics' final recommendation for regulatory action.

SUMMARY OF BIOPHARMACEUTICS FINDINGS AND RECOMMENDATION

Summary

- The results of both the fasting and fed bioequivalence studies demonstrated acceptable bioequivalence to support approval (see Biopharm-Quality Review #1).
- The following dissolution method and acceptance criteria are acceptable (see Biopharm-Quality Review #1).
    - Dissolution method: USP 2, 75 rpm, 900 mL 0.1 N HCl at 37oC
    - Acceptance criteria: Abacavir: Q = (b) (4) % in 15 minutes
      Lamivudine: Q = (b) (4) % in 15 minutes

In addition, the tablet's dissolution is not rate limiting for expiry dating.

- The bioequivalence studies (clinical and analytical portions) were inspected by the Office of Scientific Investigations. No objectionable issues were noted, and the data were found acceptable for review.

Final Recommendation

NDA 204311 for Abacavir/Lamivudine Tablets for Oral Suspension is recommended for ***TENTATIVE APPROVAL*** from the Biopharmaceutics perspective.

Administrative Block {see electronic signature page}

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MINERVA HUGHES
10/14/2014

ANGELICA DORANTES
10/14/2014

NDA 204311

Abacavir and Lamivudine Tablets for Oral Suspension

(60 mg/30 mg)

Mylan Laboratories Limited
(Nashik District, India)

Rajiv Agarwal

Review Chemist

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

CMC REVIEW OF NDA 204311
For the Division of Anti-Viral Products

Table of Contents

CMC Review Data Sheet

1. NDA 204311

2. REVIEW #: 1

3. REVIEW DATE: 15-SEP-2014

4. REVIEWER: Rajiv Agarwal, Ph.D.; Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	24-DEC-2013
Amendment	05-FEB-2014
Amendment	15-MAY-2014
Amendment	26-JUN-2014
Amendment	01-AUG-2014
Amendment	22-AUG-2014
Amendment	12-SEP-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Mylan Laboratories Limited
Address:	Plot # 564/A/22 Road # 92, Jubilee Hills Hyderabad, AP India
Representative:	Shane Shupe, Senior Manager, Regulatory Affairs, Mylan Pharmaceuticals, Inc. 781 Chesnut Ridge Road PO Box 4310 Morgantown, WV 26504-4310
Telephone:	304-554-4148 FAX: 301-285-6407

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	N/A
b) Non-Proprietary Name:	Abacavir and Lamivudine

CMC Review Data Sheet

c) Code Name/# (ONDQA only): N/A

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

11. DOSAGE FORM: Tablets for Oral Suspension (scored tablets, gives two halves)

12. STRENGTH/POTENCY: 60 mg/30 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

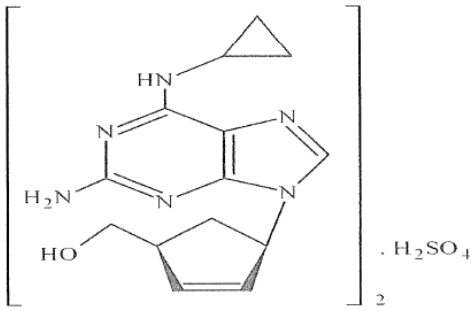
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

Abacavir Sulfate: (1S, 4R)-4-[2-Amino-6(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol hemisulfate



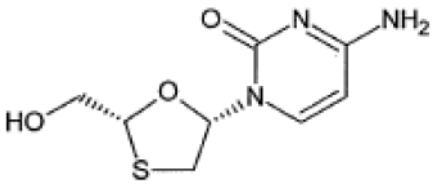
Molecular formula: $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$
Molecular weight: 670.76

Lamivudine:

2(1*H*)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yI]-, (2*R*-Cis) OR (-)-1-[*2R, 5S*)-2-(Hydroxymethyl)-1,3- oxathiolan-5-yl] cytosine,

(*2R*- Cis)-4-Amino- 1 -[2-(hydroxymethyl)- 1,3-oxathiolan- *5*- yl]-2 (1*H*)-pyrimidinone,

3TC; (-)-2'-deoxy-3'-thiacytidine.



Molecular formula: $C_8H_{11}N_3O_3S$
Molecular weight: 229.26

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		3	Adequate	24-JUL-2014	Reviewed by Dr. Bogdan Kurtyka for ANDA (b) (4) (b) (4),
	II			3	Adequate	25-OCT-2013	Reviewed by Dr. George Lunn for NDA (b) (4)
	IV			3	Adequate	16-NOV-2011	Reviewed by Dr. Xuhong Li for NDA (b) (4)
	III			4	Adequate	1-APR-2014	See the NDA review section P.7
	III			3	Adequate	7-JUL-2010	Reviewed by Dr. Caroline Strasinger for NDA (b) (4)

(b) (4)	III	(b) (4)	3	Adequate	1-MAR-2013	Reviewed by Dr. Joel Hathaway for NDA (b) (4)
	III		3	Adequate	1-MAR-2013	Reviewed by Dr. Joel Hathaway for NDA (b) (4)
	III		3	Adequate	25-OCT-2012	(b) (4)
	III		3	Adequate	24-MAR-2012	Reviewed by Dr. George Lunn for NDA (b) (4)
	III		3	Adequate	10-SEP-2013	Reviewed by Dr. Jane Chang

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	204915	Different strengths (120 mg/60 mg)

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	25-FEB-2014	Office of Compliance
EA	Categorical exclusion is requested, and granted (see review)	15-SEP-2014	Rajiv Agarwal
Quality Microbiology	Acceptable	24-JUL-2014	Dr. Stephen Langille
Biopharmaceutics	Acceptable	11-SEP-2014	Dr. Minerva Hughes

The CMC Review for NDA 204311

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC information in the NDA has been reviewed and found satisfactory. Revisions to the proposed labeling (Highlight, Description and How Supplied sections) have been conveyed to the OND PM and will be finalized during team review of the labeling

The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application.

The Product Quality Microbiology review recommends tentative approval. The Biopharmaceutics review indicates that the dissolution method and acceptance criteria are now acceptable, but that the OSI inspection report is currently pending.

Overall, the CMC recommendation is for tentative approval, provided no issues are identified in the final OSI inspection report.

Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The CMC information related to the, Abacavir Sulfate, USP and Lamivudine drug substances was cross referenced to Mylan's DMFs (b) (4) and (b) (4) respectively. The information was reviewed for DMF (b) (4) by Dr. Sukhamaya Bain of OGD on 2-JAN-2014 and for DMF (b) (4) by Dr. George Lunn of ONDQA on 25-OCT-2013 and was deemed adequate. DMF (b) (4) had an amendment submitted on 3-APR-2014 and was reviewed on 24-JUL-2014 and deemed adequate. There are no amendments to DMF (b) (4)

The open part of the two DMFs was also provided in the current NDA and are reviewed in conjunction with the original DMFs. Overall, the Chemistry,

Manufacturing, and Controls information pertaining to the drug substance is deemed adequate.

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug substance manufacturing and testing operations is Acceptable (See Attachment).

(2) Drug Product (*drug load:* (b) (4) *% abacavir;* (b) (4) *% lamivudine*)

Abacavir and Lamivudine tablets for Oral Suspension, 60 mg/30 mg are white to off white, round, (b) (4) *functionally scored tablets debossed with AL above the score and 7 below the score on one side (single score) and M on the other side of the tablet. Mylan Laboratories Limited (Nashik District, India) manufacturers the tablet drug product.*

The tablets (60 tablets) were packaged in 60 cc White Round HDPE bottle with a 33 mm Screw Closure and (b) (4) *Silica Gel Canister and* (b) (4) (b) (4) *Cotton.*

The tablets were also packaged in 60 cc White Round HDPE bottle with a 33 mm Screw Closure with (b) (4) *Cotton (does not contain Silica Gel Canister). The applicant states that this packaging configuration will be used to package the drug product for commercial distribution.*

The labeling provides the procedure for children who are unable to swallow tablets.

Abacavir and Lamivudine Tablets for Oral Suspension,60 mg/30 mg are (b) (4) (b) (4)

(b) (4)

dissolution test was evaluated during the pharmaceutical development and determined to be satisfactory.

Since the tablets are scored to provide two equal halves, studies were performed using tablets compressed to different hardness levels to evaluate the effect on tablet splitting. Per the tablet scoring guidance, the tablets halves were evaluated for content uniformity and friability (at low, medium and high hardnesses), to address both the equal distribution of drugs in the two halves (b) (4) *during splitting. The average mean* (b) (4) *is determined to be NMT* (b) (4) *%, as outlined in the tablet scoring guidance, and Friability is NMT* (b) (4) *%, confirming that the tablet performs as required upon splitting.*

All batches were tested at 30°C/75%RH (long-term) as is recommended for PEPFAR products, and accelerated conditions for description, assay, dissolution, related substances, (b) (4) *disintegration time, hardness, and* (b) (4) *tests and the results are within the proposed acceptance criteria. Both release and stability acceptance criteria are the same* (b) (4) (b) (4) (b) (4)

Results of holding time stability study was conducted on (b) (4) *tablets packaged in* (b) (4) *at 25 C/60% and were within the acceptance criteria.*

A (b) (4) *study for reconstituted suspension* (b) (4) (b) (4) *of the Abacavir Sulfate and Lamivudine Tablets for Oral Suspension was carried out and the suspension hold time stability report (Batch 2001282) is provided. The results meet the proposed acceptance criteria including the microbial limits.*

A review of the stability data did not indicate apparent trends except for a possible increase in (b) (4) *in a few bottle configurations but values remained within the acceptance criterion.*

All accelerated stability data for each of three batches were conducted for a six month period and found to be within specifications. Long-Term stability studies were conducted at 30^0C for all three batches and indicated that all parameters to be within specification limits and to be stable for 12 months.

Based upon the above stability data and minor trends, an expiration date of 24 months is recommended for this PEPFAR drug product, when stored at 30°C. (b) (4) *Since this product could be used anywhere in the world, including countries in Climatic Zone IVb (hot and very humid), the long-term condition of 30ºC/75%RH is used in the stability studies; stability under this condition is felt to support room temperature storage in all Climatic Zones.*

The applicant was asked to revise the recommended storage statement on the container/carton labels to "Store below 30ºC (86°F)" and the statement in the Prescribing Information to " (b) (4) *" and asked to provide the revised color mock ups of container and carton labels.*

The dissolution acceptance criterion was revised after recommendations from the by Quality Biopharmaceutics staff.

Upon the request of OPS Quality Microbiologist, the applicant added the microbial test at release and tested the batches at long term storage temperature for this attribute. Results were within the proposed acceptance criterion.

The final recommendation from the Office of Compliance on cGMP status of all manufacturing and testing operations is Acceptable (See Attachment).

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

The recommended oral dosage of abacavir sulfate and lamivudine in HIV-1-infected pediatric patients 3 months and older is abacavir 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) and lamivudine 4 mg/kg twice daily (up to a maximum of 150 mg twice daily) in combination with other antiretroviral agents. Dosing recommendations for the tablets for Oral Suspension are provided in Table 1.

Table 1. Dosing Recommendations for Abacavir Sulfate and Lamivudine Tablets for Oral Suspension Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Abacavir sulfate and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 - < 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 - < 12	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 - < 17	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 - < 20	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 - < 25	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 - < 29	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 - < 35	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L
≥ 35	5 tablets (300 mg A/150 mg L)	5 tablets (300 mg A/150 mg L)	600A/300L

A= abacavir sulfate; L= lamivudine

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

CMC information in the NDA has been reviewed and found satisfactory. The following non-approvability issues remains to be resolved:

- CMC recommendations have been conveyed to the OND PM, but labels and labeling of the PI are not finalized

The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application, and the Product Quality Microbiology review recommends tentative approval. The Biopharmaceutics review indicates that the dissolution method and acceptance criteria are now acceptable, but that the OSI inspection report is currently pending.

Overall, the CMC recommendation is for tentative approval, provided no issues are identified in the final OSI inspection report.

III. Life-Cycle Knowledge Management

Risk Assessment:

FROM INITIAL QUALITY ASSESSMENT	REVIEW ASSESSMENT

Executive Summary Section

Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay, Stability	(b) (4)	L	(b) (4)	**L**	***Compatibility with excipient should be demonstrated if changes are made to the quality of the excipients.*** Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes
Physical stability (solid state)		M		**L**	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes
Content uniformity		L		**L**	(b) (4) Changes in formulation or process should be assessed according to relevant SUPAC and Tablet Scoring Guidances for Post-Approval changes.
Microbial limits		L		**L**	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.
Dissolution – BCS Class I & III		L		**L**	(b) (4) Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.
Functionally Scored Tablets: Dissolution		M		**L**	Acceptable dissolution of whole tablets should be adequate since bridge to half tablet dissolution assessed in NDA. Changes in formulation or process should be assessed according to relevant SUPAC and Tablet Scoring

Executive Summary Section

FROM INITIAL QUALITY ASSESSMENT			REVIEW ASSESSMENT		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
			(b) (4)		Guidances for Post-Approval changes
Functionally Scored Tablets: Content uniformity (based on uneven split)	No spec for CU of half-tablets	M		**L**	***Spec for whole tablet should be adequate since bridge to half tablet CU assessed in NDA. Changes in formulation or process should be assessed according to relevant SUPAC and Tablet Scoring Guidances for Post-Approval changes
Functionally Scored Tablets: Friability	No spec for friability of half-tablets	M		**L**	(b) (4) Changes in formulation or process should be assessed according to relevant SUPAC and Tablet Scoring Guidances for Post-Approval changes
Disintegration (ODT)	I think disintegration is relevant for TOS	L		**L**	(b) (4) Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.
Palatability (Oral Powder, TOS, etc)		M		**L**	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes

**Risk ranking applies to product attribute/CQA*

***For example, post marketing commitment, knowledge management post approval, etc.*

*** (b) (4)

(b) (4)

(b) (4)

IV. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

B. Endorsement Block:

Rajiv Agarwal, Ph.D.; Ph.D.

(See appended electronic signature page)

Stephen Miller, Ph.D ; CMC Lead

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

C. CC Block: entered electronically in DARRTS

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(b) (4)

A APPENDICES

A.1 Facilities and Equipment (biotech only)

Not Applicable

A.2 Adventitious Agents Safety Evaluation

Not Applicable

A.3 Novel Excipients

There are no novel excipients used in the manufacturing of this drug product.

R REGIONAL INFORMATION

R1 Executed Batch Records

Executed Batch Records of Lots 2001282, 2001283, and 2001284 manufactured at Mylan in India is provided. The manufacturing process for these lots is representative of the manufacturing process described in this application. and includes the amounts of active and excipients, manufacturing equipment and ranges of operation to manufacture the drug product.

Evaluation: *This section is adequate.*

R2 Comparability Protocols

Not Applicable

R3 Methods Validation Package

The analytical procedures and their validation were reviewed and found to be adequate. Method validation packages was not sent to FDA per ONDQA policy for its evaluation.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

Note: ***The following changes/edits are made in the Highlights and Description sections and will be conveyed to the applicant by the OND.***

A. Labeling & Package Insert

1. Package Insert

a. "Highlights" Section

(b) (4)

[redacted]

Evaluation:

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	

Proprietary name and established name	Proprietary name and established name are described as: ***Abacavir and lamivudine*** **Satisfactory**
Dosage form, route of administration	**Tablets for Oral Suspension contain 60 mg of abacavir and 30 mg of lamivudine. (3)**
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	
Whether the drug product is scored	This drug product **is scored.** ***The statement is now included in this section.***

Overall evaluation: This section is now satisfactory.

(b) "Full Prescribing Information" Section

#3. Dosage Form and Strength

(b) (4)

[redacted]

Evaluation:

Item	Comments on the Information Provided in NDA
Available dosage forms and strengths: in metric system	**Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable) A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	***The equivalency statement is included in this section.*** The (b) (4) tablets are White to off white, round, (b) (4) tablet debossed with **AL** above the score

and **7** below the score on one side and **M** on the other side of the tablet.

Overall evaluation: This section is now satisfactory.

(b) (4)

Overall evaluation: With edits, this section is now satisfactory.

#11. Description

(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name and established name Dosage form and route of administration Active moiety expression of strength with equivalence statement (if applicable)	**Satisfactory** ***The equivalency statement is included in this section.***
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)).	**Satisfactory.**
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	**Satisfactory.**
Chemical name, structural formula, molecular weight	Chemical name, structural formula and molecular weight are correctly described in this section. **Satisfactory.**
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	White to yellow

Overall evaluation: *The applicant revised* (b) (4) (b) (4) *. The equivalency statement is included in this section.*

#16. How Supplied/Storage and Handling

(b) (4)

[redacted]

Evaluation:

Item	Comments on the Information Provided in NDA
Strength of dosage form	Strengths are correctly described as above **Satisfactory.**
Available units (e.g., bottles of 30 tablets)	**Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) **Satisfactory.**
Special handling (e.g., protect from light)	None
Storage conditions	**Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Stated at the end of the labeling. **Satisfactory.**

Evaluation: The "How Supplied/Storage and Handling" section is not satisfactory.

Comment: The NDC # on the bottle label and the PI is different (NDC # on the bottle is (b) (4) while NDC on the PI is (b) (4). The applicant should confirm which NDC number is correct and revise accordingly. The applicant revised the container closure via amendment dated 12-SEP-2014. Adequate.

1. Immediate container label "Trade" labels (Bottle of 60 tablets)

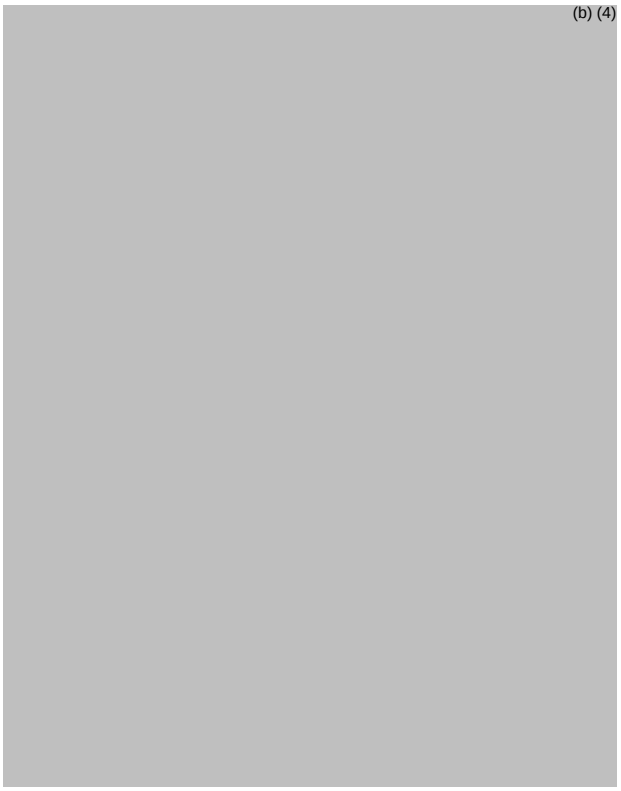
Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	**The established name presented correctly. Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strengths are correctly expressed. **Satisfactory**
Net contents (21 CFR 201.51(a))	Net content is provided **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement is now displayed **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is provided **Satisfactory**
Lot number and Expiration date (21 CFR 201.17)	Provided **Satisfactory**
Storage conditions	Provided **Satisfactory**
Bar code (21CFR 201.25)	**Provided Satisfactory**
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. **Satisfactory**
And others, if space is available	N/A

Immediate container label is now satisfactory.

2. **Secondary container label "Trade" labels (Carton of 60 tablets)**

CMC Assessment Section



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name is presented correctly. **Satisfactory**
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strengths are correctly expressed. **Satisfactory**
Net contents (21 CFR 201.51(a))	Provided **Satisfactory**
"Rx only" displayed prominently on the main panel	The statement is displayed **Satisfactory**
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	Provided (65015-231-99). **Satisfactory**
Lot number and Expiration date (21 CFR 201.17)	Provided **Satisfactory**
Storage conditions	Provided **Satisfactory**
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. **Satisfactory**
And others, if space is available	N/A

2. (b) (4)

(b) (4)

Evaluation:

(b) (4)

Overall deficiencies:

The following deficiencies were communicated to the applicant and satisfactorily responded :

Deficiencies: *Please revise the information as recommended below and provide the draft labels for review.*

- *Revise* (b) (4)
- (b) (4)
- *Revise the recommended storage statement on the container/carton labels to "Store below 30ºC (86°F)" and the statement in the PI and Medication Guide to* (b) (4)
- (b) (4)
- Amend the equivalency statement on the container/closure labels (bottle, carton (b) (4) (b) (4) labels) as follows:

  (b) (4)

- The NDC # on the bottle/carton label and the PI is different (NDC # on the bottle/carton is (b) (4) while NDC on the PI is (b) (4)). Please confirm which NDC number is correct and revise either the bottle labels (bottle and carton) or PI accordingly.

Response: *As requested, the applicant revised the container labels via amendments dated 26-JUN-2014, 1-AUG-2014.and 12-SEP-2014.* ***Adequate***

B. Environmental Assessment Or Claim Of Categorical Exclusion

In accordance with 21 CFR 25.31(b), Mylan Laboratories Ltd claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20 for approval. Mylan states that for action on an application the action does not increase the use of active ingredient.

Evaluation: Granted

III. List Of Deficiencies # 1

(communicated on 5-JUN-2014 and all but one are satisfactorily resolved on 26-JUN-2014)

Drug Product:

(b) (4)

Labeling:

Revise the container closure labels as follows and provide the revised color mock ups of container and carton labels.

- *Revise the* (b) (4) *throughout the Packaged Insert (PI) and Medication Guide as well.*
- *Revise the recommended storage statement on the container/carton labels to "Store below 30ºC (86°F)" and the statement in the PI and Medication Guide to* (b) (4)
- *Provide "Rx only" statement on the main panel of container/closure labels.*

List of Deficiencies # 2:

(Prepared by Dr. Miller in consultation with Yana Mille (OPS) and Dr. Richard Lostritto (ONDQA and communicated on 23-JUL-2014 and satisfactorily resolved on 1-AUG-2014)

1. *We request that you consider modifying the name of these two products by omitting the name of the sulfate counterion. Since all abacavir products have the strength expressed as the free base, this approach would support the adoption by USP of future drug product monographs which are fully aligned with the "Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations."*

   The USP includes official monographs for two other abacavir products: "Abacavir Tablets" and "Abacavir Oral Solution." Additionally, while not official yet, we are aware that the USP has balloted and approved the title "Abacavir and Lamivudine Tablets for Oral Solution" as a monograph title in January 2012. For reference, see the Cumulative List of Nomenclature Decisions (August 2010 to February 2014) on http://www.usp.org/usp-nf/development-process/compendial-nomenclature).

   FDA supports the approach that USP is taking, as it leads to monographs where the title and strength match. Please refer to the Dec 2013 draft guidance on Naming of Drug Products Containing Salt Drug Substances (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf)

   We recommend that you change the established names to:

   - *NDA 204-311: Abacavir and Lamivudine Tablets for Oral Solution; 60mg / 30 mg*

(b) (4)

Please submit amended container labels at this time, and make the changes in the prescribing information at an appropriate time during labeling negotiations.

(b) (4)

List of Deficiencies # 3:

(communicated on 8-AUG-2014, responses are and satisfactorily resolved on 22-AUG-2014)

1. (b) (4)

2. *NDA 204311 states that the tablets will be packaged in 60 cc White Round HDPE bottle with a 33 mm Screw Closure, liner, 1 gram Silica Gel Canister and* (b) (4) *Cotton. It also states that the tablets will be packaged in 60 cc White Round HDPE bottle with a 33 mm Screw Closure, liner and* (b) (4) *Cotton (without Silica Gel Canister). Please identify the commercial packaging.*

List of Deficiencies # 4:

(communicated on 10-SEP-2014, responses are and satisfactorily resolved on 12-SEP-2014)

1. *Amend the equivalency statement on the container/closure labels (bottle, carton and* (b) (4) *labels) as follows:*

   "Each tablet contains 60 mg of abacavir (equivalent to 70.2 mg of abacavir sulfate (b) (4) *and 30 mg of lamivudine USP"*

2. *The NDC # on the bottle/carton label and the PI is different (NDC # on the bottle/carton is* (b) (4) *while NDC on the PI is* (b) (4)*). Please confirm which NDC number is correct and revise either the bottle labels (bottle and carton) or PI accordingly.*

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAJIV AGARWAL
09/15/2014

STEPHEN MILLER
09/15/2014
I concur.

RAPTI D MADURAWE
09/15/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204311	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	23 December 2013		
Division:	Division of Antiviral Products	**Team Leader:** Angelica Dorantes, Ph.D.,	
		Acting Supervisor: Paul Seo, Ph.D.	
Sponsor:	Mylan Laboratories, Ltd.	**Secondary Reviewer:** Team Leader	
Trade Name:	TBD	**Date Assigned:**	7 Jan 2014
		Primary Review: **PDUFA Date:**	15 Sept 2014 23 Oct 2014
Generic Name:	Abacavir Sulfate and Lamivudine Scored Tablets for Oral Suspension (60/30 mg)	**Date of Review:**	11 Sept 2014
Indication:	HIV-1 infection	**Type of Submission:** **505(b)(2)** (PEPFAR)	
Dosage Form/Strengths	Tablet for oral suspension		
Route of Administration	Oral		

Biopharmaceutics Review Focus:

- Pivotal bioequivalence studies
- Dissolution method development and acceptance criteria

EXECUTIVE SUMMARY

NDA 204311 is submitted under section 505(b)(2) of the Food Drug & Cosmetics Act for the use of a functionally scored abacavir sulfate/lamivudine (60/30 mg) fixed dose combination (FDC) tablet to treat pediatric HIV patients.

SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

This Biopharmaceutics Review evaluates the pivotal bioequivalence studies, dissolution quality controls, dissolution stability, and product labeling.

Bioequivalence Studies

The Applicant conducted two *in vivo* bioequivalence studies comparing Abacavir Sulfate and Lamivudine Tablets for Oral Suspension, 60 mg/ 30 mg to the Reference Listed Drug (RLD), ZIAGEN (Abacavir Sulfate) Oral Solution 20 mg/mL (NDA #020978) and EPIVIR (Lamivudine) Oral Solution, 10 mg/mL (NDA # 020596). The studies included a single dose fasting and fed study.

(b) (4)

The results of both the fasting and fed bioequivalence studies demonstrated acceptable bioequivalence to support approval.

Dissolution Quality Controls/Stability

The following dissolution method and acceptance criteria are acceptable.

- Dissolution method: USP 2, 75 rpm, 900 mL 0.1 N HCl at 37°C
- Acceptance criteria: Abacavir: Q = (b) (4)% in 15 minutes

  Lamivudine: Q = (b) (4)% in 15 minutes

In addition, the tablet's dissolution is not rate limiting for setting an expiration dating period.

Risk Evaluation

NDA's Risk Assessment Table

From Biopharmaceutics Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments**
Dissolution	None identified	L	None	**Acceptable**	• The NDA's dissolution method and acceptance criteria were found acceptable

Labeling

There are no comments regarding the proposed labeling.

CONSULTS

The report from the Office of Scientific Investigations for the Bioequivalence studies analytical and clinical sites inspections are pending.

PHASE 4 COMMITMENTS

None.

RECOMMENDATION

NDA 204311 for Abacavir/Lamivudine Tablets for Oral Suspension is ***approvable*** from the Biopharmaceutics perspective. However, a final recommendation is pending the results of the clinical site inspections.

Administrative Block {See Appended Electronic Signature Page}

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Table of Contents

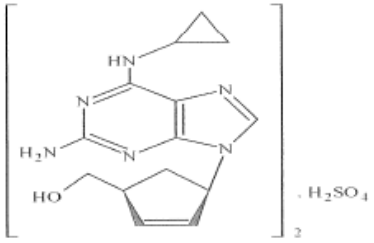
BIOPHARMACEUTICS REVIEW

1 GENERAL ATTRIBUTES

1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

- ***Drug substance highlights***

Abacavir sulfate is a synthetic nucleoside analog with the following chemical structure and formula.



$(C_{14}H_{18}N_6O)_2 * H_2SO_4$, MW = 229.26 g/mol.

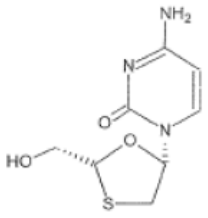
It is manufactured as a white to cream colored crystalline powder, with no known polymorphs. Based on the pH solubility profile and dose, the drug substance is considered a highly soluble drug (largest dose = 60 mg, dose/solubility = 0.78 mL).

Abacavir Sulfate Solubility Profile (25°C)

pH of the buffer	Solubility (mg/mL)
1.2	112.0
6.0	87.0
8.0	77.0

Abacavir sulfate is not hygroscopic; however, there are two chiral centers, and thus a potential for isomerization. Particle size is not controlled for in the specification and the substance is assigned a retest period of (b) (4) months.

Lamivudine is also a small molecule, which has the following chemical structure and formula.



, $C_8H_{11}N_3O_3S$; MW = 229.26 g/mol.

It is manufactured as a white to off-white solid and exhibits different polymorphic forms. (b) (4) is proposed for the subject NDA.

Similar to abacavir sulfate, lamivudine is highly soluble in aqueous media (largest dose = 30 mg, dose/solubility = 0.25 mL). The pH solubility profile is illustrated below.

Lamivudine pH Solubility Profile (25°C)

pH of the buffer	Solubility (mg/mL)
1.2	245.0
6.0	120.0
8.0	154.0

Lamivudine is also not hygroscopic, but has two chiral centers. The (b) (4) (b) (4) is manufactured. Particle size control, by using (b) (4), is included in the specification ((b) (4) µm and (b) (4) µm (b) (4)). The drug substance retest period is also (b) (4) months.

- ***Drug product highlights***

The drug product is formulated as a round, (b) (4), fixed dose combination (FDC) scored tablet for oral suspension, 60 mg abacavir (70.2 mg of the sulfate) and 30 mg lamivudine. The quantitative composition is tabulated below.

Total Composition

Component	60 mg/30 mg		Pharmaceutical Function	Quality Standards
	mg per tablet	% w/w		
(b) (4)				
Abacavir Sulfate[1,2]	70.200	(b) (4)	Active Ingredient	USP
Microcrystalline Cellulose (b) (4)			(b) (4)	NF
Sodium Stearyl Fumarate (b) (4)				NF
(b) (4)				
Lamivudine[1]	30.000	(b) (4)	Active Ingredient	USP
(b) (4)			(b) (4)	NF
				NF
(b) (4)				NF
Crospovidone (b) (4)				NF
Strawberry cream flavour permaseal (b) (4)				(b) (4)
(b) (4)				NF
Total tablet weight				**NA**
(b) (4)				

[2] 70.200 mg of Abacavir Sulfate is equivalent to 60 mg of Abacavir.

(b) (4)

Abacavir Sulfate USP is manufactured by Mylan Laboratories Limited (Unit 8), DMF Number (b) (4) and Lamivudine USP is manufactured by Mylan Laboratories Limited (Unit 1/2) DMF (b) (4). The finished product will be manufactured by Mylan Laboratories Limited, Nashik, India.

Reviewer's Comments: *The solubility information summarized in Module 2 for abacavir sulfate differs from the information in Module 3, which includes pH 4.5. At pH 4.5, the solubility is 60.69 mg/mL. Thus, the dose/solubility ratio is higher than stated, but still within the high solubility range. The drugs' pH dependent solubility is noted, but the complete protocol for the solubility studies was not provided. The Applicant is not claiming any BCS class designation and thus, additional information is not warranted. Referencing the available literature on abacavir sulfate and lamivudine, the Applicant's claim of high drug solubility is adequately supported.*

1.2 *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

Abacavir sulfate is a prodrug for abacavir, a carbocyclic synthetic nucleoside analog reverse transcriptase inhibitor (NRTI). Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate, an analogue of deoxyguanosine-5'triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA.

Lamivudine is a reverse transcriptase inhibitor and zalcitabine analog in which a sulfur atom replaces the 3' carbon of the pentose ring. It is used to treat HIV-1 and hepatitis B (HBV). Lamivudine is phosphorylated intracellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). This nucleoside analogue is incorporated into viral DNA by HIV reverse transcriptase and HBV polymerase, resulting in DNA chain termination.

The proposed indication for the Abacavir/Lamivudine 60/30 mg Tablets for Oral Suspension is for the treatment of HIV-1 infection in combination with other antiretroviral agents; the same indication as the listed products relied on for approval: ZIAGE Oral Solution EQ 20 mg Base/mL (NDA# 020978), EPIVIR Oral Solution, 10 mg/mL (NDA# 020596) (b) (4)

The suspension formulation was developed primarily for pediatric use.

1.3 *What are the proposed dosage(s) and route(s) of administration?*

The recommended oral dosage of abacavir and lamivudine in HIV-1-infected pediatric patients 3 months and older is abacavir 8 mg/kg twice daily (up to a maximum of 300 mg twice daily) and lamivudine 4 mg/kg twice daily (up to a maximum of 150 mg twice daily) in combination with other antiretroviral agents.

Dosing Recommendations for Abacavir Sulfate and Lamivudine Tablets Pediatric Patients

Weight (kg)	Dosage Regimen Using Scored Abacavir sulfate and Lamivudine Tablets for oral suspension, 60 mg/30 mg		Total Daily Dose (mg)
	AM Dose (mg)	PM Dose (mg)	
5	½ tablet (30 mg A/15 mg L)	1 tablet (60 mg A/30 mg L)	90A/45L
6 - < 9	1 tablet (60 mg A/30 mg L)	1 tablet (60 mg A/30 mg L)	120A/60L
9 - < 12	1.5 tablets (90 mg A/45 mg L)	1.5 tablets (90 mg A/45 mg L)	180A/90L
12 - < 17	2 tablets (120 mg A/60 mg L)	2 tablets (120 mg A/60 mg L)	240A/120L
17 - < 20	2.5 tablets (150 mg A/75 mg L)	2.5 tablets (150 mg A/75 mg L)	300A/150L
20 - < 25	3 tablets (180 mg A/90 mg L)	3 tablets (180 mg A/90 mg L)	360A/180L
25 - < 29	3.5 tablets (210 mg A/105 mg L)	3.5 tablets (210 mg A/105 mg L)	420A/210L
29 - < 35	4 tablets (240 mg A/120 mg L)	4 tablets (240 mg A/120 mg L)	480A/240L
≥ 35	5 tablets (300 mg A/150 mg L)	5 tablets (300 mg A/150 mg L)	600A/300L

A= abacavir sulfate; L= lamivudine

Reviewer's Comment: *The proposed labeling is based on the labeling for the* (b) (4) (b) (4) *and the referenced listed products. The two FDC tablets (NDA* (b) (4) *and this NDA) are* (b) (4) (b) (4)

1.4 ***Is there any information on BCS classification? What claim does the applicant make based on BCS classification? What data are available to support this claim?***

A BCS classification is not proposed for the drug substance or product.

2 GENERAL BIOPHARMACEUTICS (IN VIVO)

2.1 CLINICAL STUDIES

2.1.1 What are the design features of the biopharmaceutics studies used to support the proposed to-be-marketed formulation? Summary of individual study reviews provided.

Two biopharmaceutics studies were completed to support approval of the proposed to-be-marketed product.

- Study BA12101519-01, fasting bioequivalence (BE) study
- Study BA12101520-01, fed BE study

BA12101519-01 (FASTING BE)	
STUDY DESIGN	An open label, randomized, three-period, three-treatment, three-sequence, crossover, balanced, single dose oral bioequivalence study of test product Abacavir Sulfate/Lamivudine Tablets for Oral Suspension 60 mg/30 mg of Mylan Laboratories Limited, India and reference products 'EPIVIR®' (Lamivudine) Oral Solution 10 mg/mL (1 x 3 mL) and 'ZIAGEN®' (Abacavir Sulfate) Oral Solution 20 mg/mL (1 x 3 mL) from ViiV Healthcare, Research Triangle Park, USA in healthy adult human subjects under fasting conditions.

BA12101519-01 (FASTING BE)

METHODOLOGY

The order of administration was according to the randomization schedule, with an 8 day interval between each treatment. Blood samples were collected at pre-dose (0.00 hours) and at intervals over 12.00 hours after administration of each dose and analyzed using HPLC/MS.

During the course of study, safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests (hematology, biochemistry, immunological tests, urine analysis), chest X-ray (within past six months) and ECG at baseline. The serum amylase test was performed at the time of screening, prior to check in of Period II & III and at the time of the end of study laboratory assessment. Laboratory parameters (hematology and biochemistry tests) were reassessed at 12.00 hours post dose of the last study period.

Statistical analysis was performed on the pharmacokinetic data to compare the relative oral bioavailability of test formulation to the reference formulation using WinNonlin and SAS.

Bioequivalence was determined by a statistical comparison of AUCt, AUCi and Cmax for the test and reference products for Abacavir and Lamivudine. The secondary parameters of Tmax, Kel, and tHalf were also analyzed.

NUMBER OF SUBJECTS/DEMOGRAPHICS

According to the sponsor's in-house sample size estimation for crossover study, assuming a T/R ratio = 93-107%, intra-subject C.V (%) ~ 28 % for both AUC and Cmax, significance level = 5%, power = 80%, bioequivalence limits = 80.00-125.00 %, a sample size of 42 subjects was considered sufficient to demonstrate bioequivalence.

A total of 52 subjects were enrolled, and 48 were dosed with study drug. A total of 47 subjects completed the study. One subject, Subject (b) (6), was discontinued post dose Period II on medical grounds; he had an adverse event of vomiting. The subject was dosed with the Reference product (R2) in Period II.

There were no protocol deviations in the study.

FASTING BIOEQUIVALENCE STUDY
MYLAN # BA12101519-01

		Treatment Groups		
		Test Product (T) N = 47	**Reference Product (R1) N = 47**	**Reference Product (R2) N = 47**
Age (years)	Mean ± SD	31 ± 7	31 ± 7	31 ± 7
	Range	20 - 44	20 - 44	20 - 44
Age Groups	< 18	-	-	-
	18 – 40	44 (93.62%)	44 (93.62%)	44 (93.62%)
	41 – 64	3 (6.38%)	3 (6.38%)	3 (6.38%)
Sex	Male	47 (100%)	47 (100%)	47 (100%)
	Female	0 (0%)	0 (0%)	0 (0%)
Race	Asian	47 (100%)	47 (100%)	47 (100%)
BMI (Kg/m^2)	Mean ± SD	22.7 ± 3.2	22.7 ± 3.2	22.7 ± 3.2
	Range	18.6 – 29.1	18.6 – 29.1	18.6 –29.1
Other factors				
Tobacco users	Yes	0 (0.00%)	0 (0.00%)	0 (0.00%)

BA12101519-01 (FASTING BE)

	No	47 (100.00%)	47 (100.00%)	47 (100.00%)	

SUMMARY OF RESULTS

There were no blood sampling time deviations noted during the study. All values below the lower limit of quantification were considered as zero in the PK and statistical analysis.

No significant sequence or period effects were noted for either of the drugs in the study.

Abacavir

Fasted Bioequivalence Study (BA12101519-01)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90%CI**
AUCt	916.835	47	916.067	47	100.08	(93.93%; 106.64%)
AUCi	943.666	47	943.422	47	100.03	(94.00%; 106.44%)
Cmax	700.320	47	702.685	47	99.66	(92.39%; 107.51%)

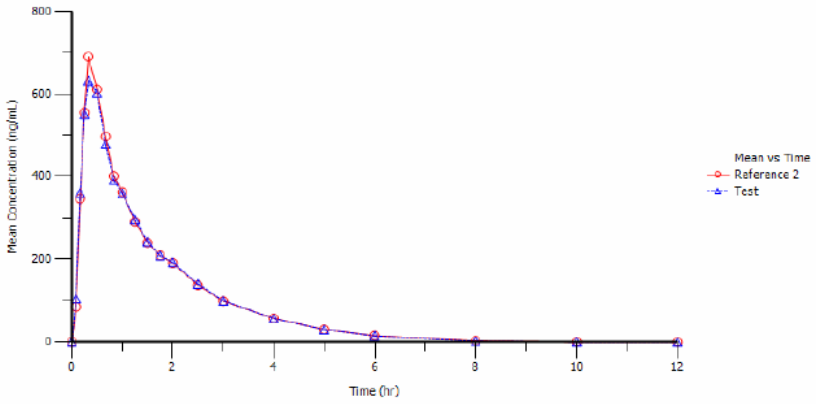
* It is noted that Subject (b) (6) was detected as an outlier in Cmax and AUC based on the Applicant's calculations (T/R >2 across all parameters), but there was not clinical reason to exclude from the data analysis. The reported results include all PK data.

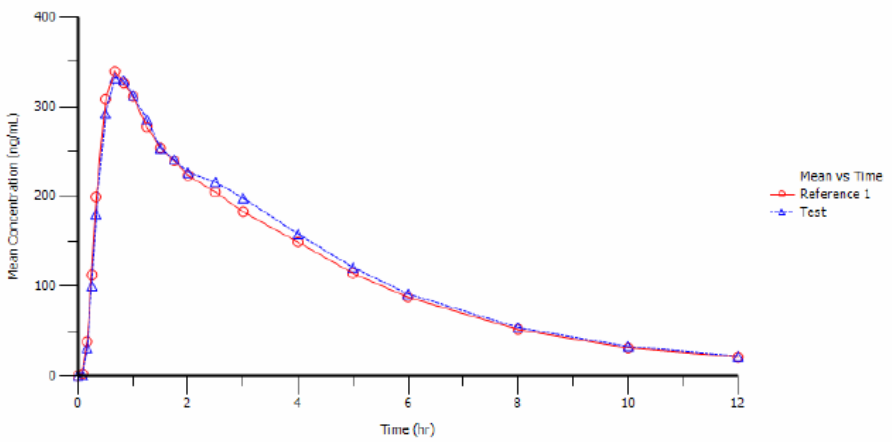
Lamivudine

Fasted Bioequivalence Study (BA12101519-01)						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90%CI**
AUCt	1383.049	47	1333.091	47	103.75	(99.36%; 108.32%)
AUCi	1477.443	47	1428.939	47	103.39	(99.32%; 107.64%)
Cmax	353.890	47	351.952	47	100.55	(93.75%; 107.84%)

Mean Plasma Concentration Profiles

Mean Plasma Concentration Profile (Abacavir)



BA12101519-01 (FASTING BE)	
	Mean Plasma Concentration Profile (Lamivudine) 
SUMMARY OF SAFETY	A total of 4 adverse events (AEs) were reported by 3 subjects during the study. All AEs were mild in severity. There were 3 AEs (vomiting (2) and amylase increased) considered possibly related to the reference product ZIAGEN® (abacavir sulfate) Oral Solution 20 mg/mL (1 x 3 mL). There was one AE (amylase increased) considered possibly related to the test product.

BA12101520-01 (FED BE)	
STUDY DESIGN	An open label, randomized, three-period, three-treatment, three-sequence, crossover, balanced, single dose oral bioequivalence study of test product Abacavir Sulfate/Lamivudine Tablets for Oral Suspension 60 mg/30 mg of Mylan Laboratories Limited, India and reference products EPIVIR (Lamivudine) Oral Solution 10 mg/mL (1 x 3 mL) and ZIAGEN (Abacavir Sulfate) Oral Solution 20 mg/mL (1 x 3 mL) from ViiV Healthcare, Research Triangle Park, USA in healthy adult human subjects under fed conditions.
METHODOLOGY	The methodology used was similar to the fasting BE study, with the exception that drug was administered 30 minutes after serving a standardized high-fat & high-calorie breakfast and there was 9 days between dosing for each period.
NUMBER OF SUBJECTS/DEMOGRAPHICS	A total of 52 healthy, adult, male human subjects were enrolled into the study to ensure the dosing of at least 48 subjects. After dosing of sufficient number of subjects in period I, the remaining four subjects were not dosed and checked out. Forty three (43) subjects completed all periods of the study and were included in the statistical analysis. - Subject (b) (6) voluntarily withdrew after dosing in period 1. - Subject (b) (6) discontinued after dosing in period 2 because of an accidental injury. - Subjects (b) (6) and (b) (6) failed to report after dosing in period 1.

BA12101520-01 (FED BE)

- Subject (b) (6) failed to report after dosing in period 2.

FED BIOEQUIVALENCE STUDY
MYLAN # BA12101520-01

		Treatment Groups		
		Test Product (T) N = 43	**Reference Product (R1) N = 43**	**Reference Product (R2) N = 43**
Age (years)	Mean ± SD	31 ± 6	31 ± 6	31 ± 6
	Range	18 - 44	18 - 44	18 - 44
Age Groups	< 18	-	-	-
	18 – 40	40 (93.02%)	40 (93.02%)	40 (93.02%)
	41 – 64	3 (6.98%)	3 (6.98%)	3 (6.98%)
Sex	Male	43 (100%)	43 (100%)	43 (100%)
	Female	0 (0%)	0 (0%)	0 (0%)
Race	Asian	43 (100%)	43 (100%)	43 (100%)
BMI (Kg/m^2)	Mean ± SD	21.9 ± 2.6	21.9 ± 2.6	21.9 ± 2.6
	Range	18.6 – 28.9	18.6 – 28.9	18.6 –28.9
Other factors				
Tobacco users	Yes	0 (0.00%)	0 (0.00%)	0 (0.00%)
	No	43 (100.00%)	43 (100.00%)	43 (100.00%)

SUMMARY OF RESULTS

The drug concentration data for all subjects who completed all the periods of study or at least two periods with one test and one reference product were included in the PK and statistical analysis.

There were two blood sampling deviations during the study (Subject (b) (6) – late on 0.083 min and missing 0.167 sample). Also, the blood samples at 0.83 min were not stored within 30 minutes for Subjects (b) (6).

Abacavir

Fed Bioequivalence Study (BA12101520-01)

Parameter	Test	N	RLD	N	Ratio	90%CI
AUCt	823.892	43	829.519	43	99.32%	(90.27%; 109.28%)
AUCi	849.308	43	860.244	43	98.73%	(89.91%; 108.41%)
Cmax	276.337	43	302.270	43	91.42%	(81.11%; 103.04%)

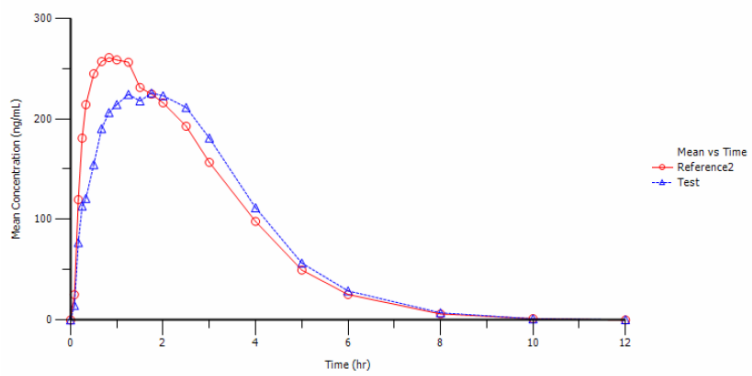
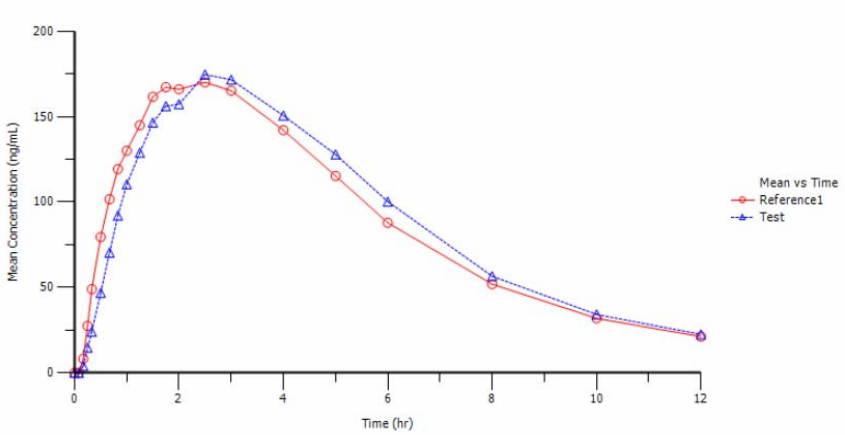
A significant sequence effect was observed for Cmax at the 10% significant level. Since there was no pre-dose concentration found in period 2 and 3 and there was an adequate wash out period (9 days), the cause for the observation is unknown.

Lamivudine

Fed Bioequivalence Study (BA12101520-01)

Parameter	Test	N	RLD	N	Ratio	90%CI
AUCt	1062.315	43	1040.431	43	102.10%	(99.63%; 104.64%)
AUCi	1155.889	43	1131.479	43	102.16%	(99.86%; 104.51%)
Cmax	185.347	43	183.846	43	100.82%	(96.55%; 105.27%)

A significant period effect was observed for the primary PK parameters and

BA12101520-01 (FED BE)	
	Tmax (see full CSR). However, no appreciable differences in food administration and dosing were noted.
Mean Plasma Concentration Profiles	**Mean Concentration Plasma Profile (Abacavir)**  **Lamivudine Mean Concentration Plasma Profile** 
SUMMARY OF SAFETY	A total of four (4) adverse events were reported by four (4) subjects during the entire study. All AEs were mild in severity. There was one (1) AE (vomiting) considered possibly related and one (1) AE (monocyte count increased) considered remotely related to the reference product R1 [EPIVIR (Lamivudine) Oral Solution 10 mg/mL (1 x 3 mL)]. There was one (1) AE (accidental injury) considered not related and one (1) AE (blood bilirubin increased) considered remotely related to the oral administration of reference product R2 [ZIAGEN (Abacavir Sulfate) Oral Solution 20 mg/mL (1 x 3 mL)].

Reviewer's Evaluation: ACCEPTABLE BIOEQUIVALENCE

Both the fasting and fed bioequivalence studies were executed using acceptable protocols for demonstrating bioequivalence (e.g., sample size, dosing schedule, washout period, statistical method). There were no observed deviations in any study that could impact study outcomes and the justifications provided for excluding any subject data from the PK analysis are acceptable (i.e., incomplete data, emesis, etc.).

Under fasting conditions, sequence or period effects were not observed during the study. Further, all drug concentration data for subjects who completed the study, including the data for Subject (b) (6), who had a T/R response that was significantly different than all other subjects (i.e., statistical outlier), were included in the analysis. There were no adverse events reported for Subject (b) (6). The geometric mean ratios (T/R) for all bioequivalence parameters were approximately 1 and the 90% confidence intervals were within the 80 – 125% bioequivalence limit. There were also no notable observations in the shape of the plasma concentration profiles.

Under fed conditions, the geometric mean ratios (T/R) and 90% confidence interval for the bioequivalence parameters also met the required 80%-125% limit for each drug. However, it was noted that the abacavir rate of exposure, as determined by Tmax, was different between the test and reference. In addition, the lower bound of the abacavir Cmax confidence interval was close to 80% and a significant sequence effect in Cmax was also noted for abacavir. This Reviewer agrees with the Applicant's conclusion that these observations do not undermine the bioequivalence finding. The root cause of the observed sequence effect is unclear; however, the elimination half-life for abacavir and lamivudine is approximately 1.5 h and 5-7 hours, respectively with supports a washout period of at least 8 days to address any carry over type effects. There were also no apparent inconsistencies in food administration.

A bioequivalence assessment using the Applicant supplied abacavir concentration data was performed by this Reviewer, which also verifies abacavir bioequivalence.

Fed Bioequivalence Study (BA12101520-01) – Reviewer's Reanalysis of Average Bioequivalence (Abacavir) Geometric Least Mean Squares						
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90%CI**
AUCt	823.79	43	829.52	43	.993	(90.27, 109.28)
AUCi	849.30	43	860.24	43	.987	(89.91, 108.41)
Cmax	276.34	43	302.26	43	.914	(81.11, 103.04)

The shift in Tmax (RefGeoLSM =0.82, TestGeoLSM =1.26 – Reviewer's Values) (RefArithMean = 1.14, TestArithMean = 1.52 – Applicant's Values), though statistically significant is nominally small, and is not considered clinically relevant given the observed inter-subject variability, the chronic dosing regimen, and the products intended use for HIV treatment.

Thus, in conclusion the overall bioequivalence data are acceptable.

2.1.2 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

The proposed product demonstrated acceptable bioequivalence to the reference listed drug products.

2.1.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

There are no proposed changes to the approved RLD labeling with regards to food. The drug product may be taken without regards to food. Acceptable bioequivalence was demonstrated under both fasting and fed conditions.

2.2 BIOANALYTICAL METHOD SECTION

2.2.1 How are the active moieties and/or metabolites identified and measured in the plasma in the biopharmaceutics studies?

In vivo analysis is based on the measured amounts of abacavir and lamivudine in plasma using a validated HPLC/MS method.

2.2.2 What bioanalytical methods are used to assess concentrations?

HPLC/MS method (b) (4)-127-00 was developed for the determination of avcavir and lamivudine in human plasma.

2.2.2.1 What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ULOQ, and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.?

The validation results are summarized below.

Abacavir Analysis	
Information Requested	**Data**
Bioanalytical method validation report location	Module: 5314-Bioanalytical Method Validation, Appendix-16.5 Bioanalytical Report, Attachment-5
Analyte	Abacavir
Internal standard (IS)	Abacavir D4
Method description	Solid Phase Extraction (method description is detailed in method (b) (4) attached as Attachment-2 to Bioanalytical Report)
Limit of quantitation	9.993 ng/mL
Average recovery of drug (%)	78.54% (LQC), 73.95% (M1QC), 74.50% (M2QC) & 78.07% (HQC)
Average recovery of IS (%)	85.03%
Standard curve concentrations (units/mL)	9.993, 19.986, 79.943, 299.786, 799.430, 1598.861, 2398.291, 3197.721, 3997.152 ng/mL
QC concentrations (units/mL)	9.989 ng/mL (LLOQ), 29.966 ng/mL (LQC), 719.180 ng/mL (M1QC) 1438.360 ng/mL (M2QC) 3036.537 ng/mL (HQC)

Abacavir Analysis	
Information Requested	**Data**
P&A 1 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 0.94% to 3.38% 99.62% to 112.16%
P&A 2 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 1.23% to 8.77% 95.84% to 101.25%
P&A 3 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 0.83% to 6.69% 96.47% to 100.43%
P&A 4 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 1.10% to 6.76% 95.82% to 99.10%
QC Interday precision range (%)	1.89% to 8.49%
QC Interday accuracy range (%)	97.26% to 101.37%
Bench-top stability (hrs)	Approx. 28 hrs 40 min @ room temperature
Stock stability (days)	Drug - 52 days (Diluent-1) & 14 days (Diluent-2) at 2-8ºC ISTD- 17 days (Diluent-1) & 15 days (Diluent-2) at 2-8ºC
Processed stability (hrs)	Refrigerator Stability in Matrix Approx. 29 hrs 57 min at 2-8ºC Dry Extract Stability approx. 30 hrs 27 min at 2-8ºC Auto Sampler Stability Approx. 68 hrs 55 min at 10ºC
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	63 days@ -20±5ºC and -70±15ºC
Dilution integrity	1/2 dilution – 2.05% (precision), 1/2 dilution – 104.95% (accuracy) 1/4 dilution – 0.77% (precision) 1/4 dilution – 97.16% (accuracy)
Selectivity	No interfering peaks noted in blank plasma samples
Instrument Ruggedness **	
P&A 1 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 1.53% to 4.07% 98.50% to 106.17%
P&A 2 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 0.53% to 3.58% 98.37% to 109.48%
QC Interday precision range (%)	1.09% to 3.99%
QC Interday accuracy range (%)	98.43% to 107.82%

Lamivudine Analysis	
Information Requested	**Data**
Bioanalytical method validation report location	Module: 5314-Bioanalytical Method Validation, Appendix-16.5 Bioanalytical Report, Attachment-5
Analyte	Lamivudine
Internal standard (IS)	Lamivudine 13CD2 15N2
Method description	Solid Phase Extraction (method description is detailed in method (b) (4) attached as Attachment-2 to Bioanalytical Report)

Lamivudine Analysis	
Information Requested	**Data**
Limit of quantitation	4.998 ng/mL
Average recovery of drug (%)	74.86% (LQC), 72.30% (M1QC), 69.86% (M2QC) & 71.78% (HQC)
Average recovery of IS (%)	79.50%
Standard curve concentrations (units/mL)	4.998, 9.997, 39.987, 99.969, 249.921, 499.843, 699.780, 959.698, 1199.622 ng/mL
QC concentrations (units/mL)	5.000 ng/mL (LLOQQC), 15.000 ng/mL (LQC), 219.996 ng/mL (M1QC) 449.993 ng/mL (M2QC) 919.985 ng/mL (HQC)
P&A 1 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 1.36% to 6.62% 93.02% to 101.87%
P&A 2 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 0.98% to 9.36% 95.28% to 106.14%
P&A 3 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 0.75% to 5.18% 94.99% to 104.49%
P&A 4 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 0.88% to 5.96% 95.50% to 104.58%
QC Interday precision range (%)	1.59% to 7.12%
QC Interday accuracy range (%)	95.40% to 103.23%
Bench-top stability (hrs)	Approx. 28 hrs 40 min @ room temperature
Stock stability (days)	Drug - 52 days (Diluent-1) & 14 days (Diluent-2) at 2-8ºC ISTD- 17 days (Diluent-1) & 15 days (Diluent-2) at 2-8ºC
Processed stability (hrs)	Refrigerator Stability in Matrix Approx. 29 hrs 57 min at 2-8ºC Dry Extract Stability approx. 30 hrs 27 min at 2-8ºC Auto Sampler Stability Approx. 68 hrs 55 min at 10ºC
Freeze-thaw stability (cycles)	5 cycles
Long-term storage stability (days)	63 days@ -20±5ºC and -70±15ºC
Dilution integrity	1/2 dilution – 3.00% (precision), 1/2 dilution – 101.53% (accuracy) 1/4 dilution – 0.60% (precision) 1/4 dilution – 104.00% (accuracy)
Selectivity	No interfering peaks noted in blank plasma samples
Instrument Ruggedness **	
P&A 1 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 1.21% to 4.27% 92.96% to 103.30%
P&A 2 **QC Intraday precision range (%)** **QC Intraday accuracy range (%)**	 0.64% to 3.57% 93.38% to 107.46%
QC Interday precision range (%)	0.96% to 4.26%

Lamivudine Analysis	
Information Requested	**Data**
QC Interday accuracy range (%)	93.17% to 103.78%

2.2.2.2 What is the QC sample plan?

QC samples were prepared in bulk by mixing an appropriate portion of the QC solutions for each active with blank human plasma. Six sets at concentration I the low, mid, and high range of the standard curve were analyzed and an additional six sets stored to evaluate long term stability.

For study BA 12101519-01, the incurred sample analysis was performed on >10% of the total samples and a total of 100% and 98.5% of abacavir and lamivudine samples, respectively, were within +/-20% of the original assay values.

For study BA 1201520-01, 276 samples were analyzed from random subjects, and a total of 97.83% and 99.45% of abacavir and lamivudine samples were found to be within +/- 20% of the original assay values.

2.2.2.3 Are the Inspection reports of the BE study acceptable?

The Report from the OSI for the BE studies is **Pending**.

3 GENERAL BIOPHARMACEUTICS (IN VITRO)

3.1 DISSOLUTION INFORMATION

3.2 DISSOLUTION METHOD

3.2.1 What is the proposed dissolution method?

A single dissolution method is proposed for both actives in the FDC table.

- USP II, 75 rpm, 900 mL 0.1N HCl at 37^{o}C

The proposed testing conditions align with those recommended in the FDA dissolution method database for abacavir and lamivudine products.

3.2.2 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The following data are provided to support the adequacy of the proposed dissolution method.

(b) (4)

(b) (4)

Reviewer's Comment: (b) (4) *Therefore, 75 rpm is acceptable in this instance.*

3.2.3 What data are available to support the discriminating power of the method?

The ability of the proposed dissolution method to detect undesired manufacturing process changes was assessed as follow.

(b) (4)

Overall, the method development studies failed to show that the dissolution method could detect undesired process variations. The Applicant stated that this

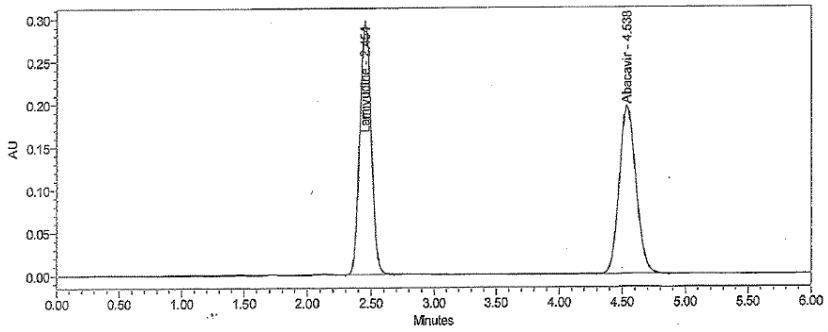
limitation is due to the highly soluble actives in the formulation as well as the tablet design as a dispersible tablet, with complete disintegration in (b) (4) minutes.

3.2.4 What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

An HPLC method was developed for dissolution analysis (isocratic, λ = 272 nm). The method was validated for precision, specificity, linearity, accuracy, solution stability, mobile phase stability, filter interference and robustness (No. ABL-DIT-DS-02/00). All analyses met the pre-specified criteria, which appear reasonable for the proposed method. However, reference is made to the Product Quality review by Rajiv Agarwal for a complete assessment.

A representative chromatogram is illustrated below.

Figure 4A: Typical chromatogram of Test solution (Method precision)



3.2.5 Is the proposed dissolution method biorelavant? What data are available to support this claim?

No, the proposed method is not linked to in vivo performance.

3.2.6 Is the proposed method acceptable? If not, what are the deficiencies?

Yes, the proposed method is acceptable. Developing a discriminating dissolution method for a fast disintegrating tablet with highly soluble drugs is a common challenge. In these cases, disintegration is often more sensitive to manufacturing changes.

3.3 ACCEPTANCE CRITERIA

3.3.1 What are the proposed dissolution acceptance criteria for this product?

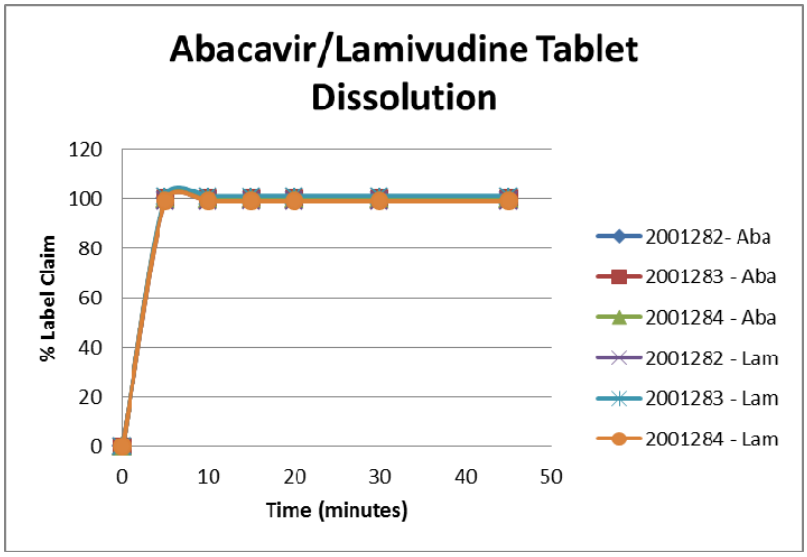
The proposed dissolution acceptance criteria are summarized below.

- Abacavir: Q = (b) (4) % at (b) (4) minutes
- Lamivudine: Q = (b) (4) % at (b) (4) minutes

3.3.2 What data are available to support the criteria?

The Applicant stated that the proposed acceptance criteria are appropriate for an immediate release dosage form and takes into account the product's dissolution profile. A clear justification was not provided.

This Reviewer notes, however, that the mean dissolution results collected during method development and for the clinical and registration lots demonstrated (b) (4)% dissolution in (b) (4) minutes for both actives and across all batches tested. Further, the tablet is (b) (4) See Reviewer generated figure using the Applicant's supplied mean dissolution data for the primary stability and clinical batches below.



(b) (4)

Regarding dissolution stability, a shelf life of 24 months is proposed. Stability data are submitted for product packaged in:

- 60 ct HDPE bottles w/ desiccant (9 months long term and 24 weeks accelerated)
- 60 ct bottles w/ void filler (9 months long term and 24 weeks accelerated)
- (b) (4)

Under accelerated conditions, all dissolution values are between (b) (4)% for abacavir and (b) (4)% for lamivudine at (b) (4) minutes. Under long term storage conditions, all values are between (b) (4)% for abacavir and (b) (4)% for lamivudine at (b) (4) minutes sampling. Although a (b) (4) minute sampling time point was not collected on stability, the totality of the data strongly suggest that dissolution is

essentially complete within (b) (4) minutes. More specifically, see the mean dissolution profile data (n=12) at release (above figure) that was reported for all three registration batches at release.

Therefore, the available data support the standard criteria for rapidly dissolving tablets of Q = (b) (4) % in 15 minutes.

Reviewer's Comment: From the biopharmaceutics perspective, the absence of a 15 minute sampling time point does not preclude granting the requested expiry period for this product, if appropriate based on the other CMC attributes (see Product Quality Review for shelf-life recommendation). The mean dissolution was consistently around (b) (4) % at (b) (4) minutes, which does not suggest any significant shift in dissolution performance even though the final sampling with not optimal. Additional dissolution data at (b) (4) minutes will be collected as part of the Applicant's post approval stability commitment and subject to ongoing FDA review as part of the product's life cycle. Annual stability surveillance is an appropriate management of the dissolution stability risks for this product based on the product's characteristics.

3.3.3 Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?

Yes.

3.3.4 Are mean (n =12) dissolution profile data used for the setting of the acceptance criteria?

Yes.

3.3.5 Are the acceptance criteria acceptable? If not, what are the recommended criteria?

The proposed acceptance criteria of Q = (b) (4) % in (b) (4) minutes for abacavir and lamivudine is not acceptable and a limit of Q = (b) (4) % in 15 minutes was recommended.

The Applicant agreed to FDA's recommended dissolution acceptance criteria in NDA amendment 22 August 2014, which includes a revised drug product specification table. The final dissolution acceptance criteria recommended for approval are:

- Abacavir: Q = (b) (4) % in 15 minutes
- Lamivudine: Q = (b) (4) % in 15 minutes

4 DISSOLUTION APPLICATIONS

4.1 FORMULATION CHANGES

4.1.1 Is the to-be-marketed formulation the same as the formulation used in the pivotal clinical or bioequivalence studies? If not, is dissolution used to bridge the data?

Yes, the to-be-marketed formulation and the formulation used in the bioequivalence studies are the same.

4.1.2 Is the finished tablet scored? Do the dissolution data comparing the split versus whole tablet support tablet splitting?

The finished tablet includes a functional score (single bisect). Divisibility data, which included the complete dissolution profile data on the sub-divided tablet, were submitted. The mean dissolution was (b) (4)% at (b) (4)minutes for the subdivided halves, which was consistent with the whole tablet.

Additionally, a 90-day in use stability study on the split tablet portions was completed. Dissolution sampling occurred at (b) (4)minutes because that was the criterion at the time of the study. All individual units were (b) (4)% dissolved at (b) (4) minutes at all-time points.

It was noted that several individual unit tablets had dissolution results up to (b) (4)%. Individual dissolution results exceeding (b) (4)% was also observed during whole tablet release and stability testing. This issue was raised with the Applicant and the CMC Reviewer and determined not to present or reflect a significant quality risk for the product.

4.2 BIOWAIVERS

4.2.1 Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

Not applicable.

4.2.2 Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

Not applicable.

4.3 IVIVC

4.3.1 Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?

Not applicable.

4.4 SURROGATES IN LIEU OF DISSOLUTION

4.4.1 Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

There are no tests being proposed as surrogates for dissolution; however, disintegration is included in the drug product specification. The disintegration test follows the general procedure "Disintegration time – Ph.Eur. and is performed at 15-25 ºC.

The proposed acceptance criterion is NMT (b) (4) minutes.

Reviewer's Evaluation: *The proposed product complies with the criteria, as per the ICH Q4B annex, for the interchangeable use of Ph. Eur. and USP <701>. In addition, the proposed acceptance criterion is adequately supported by the pharmaceutical development and product performance data.*

4.5 DISSOLUTION AND MANUFACTURING PROCESSES

4.5.1 QBD

4.5.1.1 Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

Not applicable.

4.5.1.2 Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution?

Not applicable.

4.5.1.3 What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

Not applicable.

4.5.1.4 Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

Not applicable.

4.5.2 Non-QBD

4.5.2.1 Was dissolution used to support manufacturing process/formulation development?

The finished FDC tablets are manufactured using (b) (4)

During product development, the critical quality attributes (CQAs) identified based on the severity of the harm to a patient as a result of failing to meet the quality attribute were content uniformity, dissolution, and related substances.

A summary of the Applicant's initial risk assessment of the drug substance attributes, formulation and process impact on dissolution is provided below.

Initial risk assessment of the drug substance attributes

	Particle size distribution		Solubility		Residual solvents		Chemical stability	
	Abacavir	Lamivudine	Abacavir	Lamivudine	Abacavir	Lamivudine	Abacavir	Lamivudine
Content uniformity	Low	Medium	Low	Low	Low	Low	Low	Low
Dissolution	Low	Low	Low	Low	Low	Low	Low	Low
Related substances	Low	Low	Low	Low	Low	Low	Medium	Medium

Low Medium High

Initial risk assessment of the formulation variables

Drug product CQA	MCC	Crospovidone	Sucralose	Strawberry flavor	Sodium stearyl fumarate	Drug substance PSD	
						Abacavir sulfate	Lamivudine
CU	Low	Low	Low	Low	Low	Low	Medium
Dissolution	Low	High	Low	Low	Low	Low	Low
Related substances	Low	Low	Low	Low	Low	Low	Low

Initial risk assessment of the manufacturing process

(b) (4)

As such, development studies were completed to evaluate both the formulation and process change impact dissolution and disintegration times.

4.5.2.2 What raw materials and process variables are identified as having an impact on dissolution?

Based on the results of additional testing to evaluate the potential risks summarized in Section 4.5.2.1, the final risk assessment for the impact of the different attributes and process changes on dissolution is LOW.

Thus, there is no apparent material or process variable that seems to have a significant impact on dissolution from the biopharmaceutics perspective. A full evaluation of the drug product design and process controls will be addressed by the assigned CMC Reviewer.

4.5.2.3 What is the risk assessment/studies performed to evaluate the criticality of dissolution?

Drug Substance

(b) (4)

Formulation

(b) (4)

(*Reviewer's generated graph below illustrating* (b) (4)

(b) (4)

(b) (4)

Reviewer's Evaluation: (b) (4) *From the biopharmaceutics perspective, the approach appears reasonable. However, a complete review of the process information, accounting for all CQA's, not just dissolution is deferred to the assigned CMC Reviewer.*

5 LABELING

The proposed changes to the labeling are (b) (4) (b) (4) and this Reviewer has no additional comments.

6 INFORMATION REQUESTS DURING THE REVIEW

The following information requests were issued during the NDA review cycle. Responses are incorporated into the QBR above. There are no outstanding review issues.

(b) (4)

(b) (4)

This Reviewer's comments to the Applicant were consolidated with NDA 204915, abacavir/lamivudine 120/60 mg (double scored) Tablets for Oral Suspension, where overlapping issues were noted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MINERVA HUGHES
09/11/2014

ANGELICA DORANTES
09/11/2014

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 23 July 2014

TO: NDA 204311

FROM: Stephen E. Langille, Ph.D.

THROUGH: Bryan Riley, Ph.D.

cc: Monica Zeballos
Regulatory Project Manager
OMPT/CDER/OND/OAP/DAVP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Abacavir Sulfate and Lamivudine (b) (4) scored Tabs for Oral Suspension, 60mg/30mg [Submission Date: 23 December 2013]

The Microbial Limits specification for Abacavir Sulfate and Lamivudine Scored Tab for Oral Suspension (60mg/30mg) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Abacavir Sulfate and Lamivudine Scored Tab for Oral Suspension (60mg/30mg) is a scored tab for oral administration. According to the product label, the tablet is to be suspended in two teaspoons of drinking water and administered within (b) (4).

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

M E M O R A N D U M

Microbial limits Specification for Abacavir Sulfate and Lamivudine Scored Tab for Oral Suspension (60mg/30mg)

Test	Specification
Total aerobic microbial count	No more than (b) (4) CFU/g
Total Combined yeast and mold count	No more than 100 CFU/g
E. coli	Absent

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61>and <62>.

The drug product will also be tested for Microbial Limits (b) (4) as part of the post-approval stability protocol.

ADEQUATE

Reviewer Comments – The following information request was provided to the applicant on 27 May 2014:

(b) (4)

2. (b) (4)

M E M O R A N D U M

(b) (4)

The applicant responded to this information request on 26 June 2014 with a commitment to conduct microbial limits testing at release and as part of the stability program. The microbiological quality of the drug product is controlled (b) (4)

END

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/s/

STEPHEN E LANGILLE
07/23/2014

BRYAN S RILEY
07/24/2014
I concur.

NDA 204-311 Abacavir & Lamivudine Tablets for Oral Suspension, 60mg/30mg
Applicant: Mylan Laboratories

Submission: Dec 23, 2013
DARRTS date: Sept 15, 2014
PDUFA: Oct 23, 2014

Background:
At the time the original IQA was written, an initial risk assessment table was not included. The initial risk assessment tablet below was created to conform to the recommendation that a FMECA-type table be created for NDAs for which the primary reviews are due in DARRTS after Aug 1, 2014. See Dr. Furness's email of June 16, 2014.

This document should be read in conjunction with the notes in the CMC/BP IQA for this NDA (see DARRTS).

Summary:
- Drug substance:
  - Abacavir sulfate: high solubility (BCS); non hygroscopic; single polymorphic form reported.
  - Lamivudine: high solubility (BCS); non hygroscopic; 2 (b) (4) forms known and (b) (4) are highly soluble by BCS; Mylan's process produces (b) (4) DS specification includes (b) (4)
- Stability:
  - APIs: refer to DMFs; both APIs are expected to be stable at room temp based on past experience
  - DP: very stable; total impurities increases from (b) (4)% at release to (b) (4)% after (b) (4) (b) (4) (b) (4).
- Formulation: (b) (4)% abacavir sulfate; (b) (4)% lamivudine
- Process: Abacavir sulfate (b) (4) . The lamivudine, (b) (4)
- Container closure system: HDPE bottles of 60 with or without desiccant; not clear if induction seal or CR caps; (b) (4)

Product Design FMECA for Abacavir & Lamivudine Tablets for Oral Suspension

(60 mg / 30 mg strength with single score)

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	FMECA RPN	Comment
Assay, Stability	1	2	1	**2**	
Physical stability (solid state)	4	2	4	**32**	Multiple forms of Lamiv (b) (4) However very soluble
Content uniformity	2	3	4	**24**	(b) (4)
Microbial limits	1	2	5	**10**	Not in DP spec
Dissolution – BCS Class I & III	3	2	2	**12**	Unknown if "multiple aberrant formulations" were studied
Functionally Scored Tablets: Dissolution	3	2	5	**30**	No spec for dissol of half-tablets
Functionally Scored Tablets: Content uniformity (based on uneven split)	4	2	5	**40**	No spec for CU of half-tablets
Functionally Scored Tablets: Friability	2	3	5	**30**	No spec for friability of half-tablets
Disintegration (ODT)	3	2	3	**18**	I think disintegration is relevant for TOS
Palatability (Oral Powder, TOS, etc)	3	3	5	**45**	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

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/s/

STEPHEN MILLER
07/21/2014

RAPTI D MADURAWE
07/22/2014