CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204311Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 13, 2023

To: Monica Zeballos, Sr. Program Consultant
Division of Antivirals (DAV)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ABACAVIR and LAMIVUDINE tablets for oral suspension

NDA: 204311

Background:

In response to DAV's consult request dated December 6, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), carton and container labeling, and Warning Card, for the original NDA submission for abacavir and lamivudine tablets for oral suspension.

PI/Medication Guide/IFU/Warning Card:
OPDP's review of the proposed PI and Warning Card is based on the draft labeling emailed to OPDP on December 6, 2023, and we do not have any comments at this time on the PI; we have one comment below on the Warning Card.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide/IFU, and comments were sent under separate cover on December 11, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on December 6, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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/s/

WENDY R LUBARSKY
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 11, 2023
To:	Monica Zeballos, PharmD Senior Program Consultant **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name; Dosage Form and Route:	ABACAVIR and LAMIVUDINE tablets for oral suspension
Application Type/Number:	NDA 204311
Applicant:	Mylan Laboratories Limited c/o Mylan Pharmaceuticals Inc.

1 INTRODUCTION

On June 22, 2023, Mylan Laboratories Limited c/o Mylan Pharmaceuticals Inc. submitted for the Agency's review an original 505 (b)(2) Class 2 resubmission to their proposed New Drug Application (NDA) 204311 for ABACAVIR and LAMIVUDINE tablets for oral suspension in response to the Agency's Complete Response (CR) letter dated January 13, 2023.

With this resubmission, the Applicant also requests final approval of the NDA, which references (b) (4) The Applicant proposes ABACAVIR and LAMIVUDINE tablets for oral suspension in combination with other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in pediatric patients aged 3 months and older or weighing at least 5 kg.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on December 6, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ABACAVIR and LAMIVUDINE tablets for oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU is forthcoming.

2 MATERIAL REVIEWED

- Draft ABACAVIR and LAMIVUDINE tablets for oral suspension MG and IFU received on July 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on December 6, 2023.
- Draft ABACAVIR and LAMIVUDINE tablets for oral suspension Prescribing Information (PI), received on July 15, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on December 6, 2023.
- Approved (b) (4) TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension comparator labeling dated December 10, 2021, and June 15, 2023, respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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LAURIE J BUONACCORSI
12/11/2023 08:14:19 AM

WENDY R LUBARSKY
12/11/2023 02:08:18 PM

LASHAWN M GRIFFITHS
12/12/2023 07:09:24 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 15, 2023
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 204311
Product Name and Strength:	Abacavir and Lamivudine Tablets, for Oral Suspension, 60 mg/30 mg
Applicant/Sponsor Name:	Mylan Laboratories Limited
TTT ID #:	2022-587-1
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

On June 22, 2023, the Applicant submitted a Complete Response (CR) amendment to NDA 204311. This submission referenced previously submitted container label and carton labeling dated July 15, 2022. The Division of Antivirals (DAV) requested that we review the CR response to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

We note that the previously submitted container label and carton labeling dated July 12, 2022 were found acceptable by DMEPA[a]. DMEPA will collaborate with DAV to revise the PI to address any vulnerabilities to medication error. We have no recommendations at this time.

[a] Fanari, M Label, Label and Labeling Review for Abacavir and Lamivudine Tablets (NDA 204311). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 Nov 28. RCM No.: 2022-587.

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/s/

MELINA N FANARI
09/15/2023 09:14:52 AM

MADHURI R PATEL
09/15/2023 11:40:50 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 28, 2022
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 204311
Product Name and Strength:	Abacavir and Lamivudine Tablets, for Oral Suspension, 60 mg/30 mg
Applicant/Sponsor Name:	Mylan Laboratories Limited
TTT ID #:	2022-587
DMEPA 1 Safety Evaluator:	Melina Fanari, R.Ph
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, carton labeling, warning card, Prescribing Information (PI), Instruction for Use (IFU) and Medication Guide (MG) received on July 15, 2022 for Abacavir and Lamivudine Tablets. These were submitted as part of the July 15, 2022 Complete Response (CR) amendment to NDA 204311. The Division of Antivirals (DAV) requested that we review the revised container label and carton labeling for Abacavir and Lamivudine Tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations from the July 15, 2022 CR, however, we have an additional recommendations to the prescribing information at this time and will collaborate with DAV to revise the PI as outlined below (see section 3).

[a] Wilson, V. Label, Labeling and URRA Review for Abacavir and Lamivudine Tablets (NDA 204311). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jul 12. RCM No.: 2019-312, 2019-842.

3 RECOMMENDATIONS FOR DIVISION OF ANTIVIRAL (DAV)

The total daily dose column in Table 1 of section 2.2 of the PI should be separated from the twice daily dosing regimen header and relocated to after the weight column.

APPENDIX A. LIST OF LABELS AND LABELING REVIEWED

A.1 Prescribing Information, Instruction for Use and Medication Guide (Images not shown) received on July 15, 2022, available at: \\CDSESUB1\evsprod\NDA204311\0034\m1\us\114-labeling\draft\labeling

A.2 IMAGES OF CARTON LABEL AND CONTAINER LABELING

Container labels

Carton labeling

Warning Card

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/s/

MELINA N FANARI
11/28/2022 09:19:12 AM

MADHURI R PATEL
11/28/2022 02:37:16 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 26, 2019
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	Abacavir and Lamivudine
Dosage Form and Route:	tablets for oral suspension
Application Type/Number:	NDA 204311
Applicant:	Mylan Laboratories Limited, India

1 INTRODUCTION

On February 6, 2019, Mylan Laboratories Limited, India submitted for the Agency's review a 505(b)(2) Class 2 resubmission to their New Drug Application (NDA) 204311 for Abacavir and Lamivudine tablets for oral suspension. The reference listed drug (RLD) for this application is (b) (4) (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on July 11, 2019 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Abacavir and Lamivudine tablets for oral suspension.

2 MATERIAL REVIEWED

- Draft Abacavir and Lamivudine tablets for oral suspension MG received on February 6, 2019, and received by DMPP and OPDP on July 11, 2019.
- Draft Abacavir and Lamivudine tablets for oral suspension Prescribing Information (PI) received on February 6, 2019, revised by the Review Division (b) (4)

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
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WENDY R LUBARSKY
07/26/2019 11:30:30 AM

LASHAWN M GRIFFITHS
07/26/2019 12:03:07 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 25, 2019

To: Monica Zeballos, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for ABACAVIR and LAMIVUDINE tablets for oral suspension, for oral use

NDA: 204311

In response to DAVP consult request dated July 11, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Warning Card, and carton and container labeling for the original NDA submission for ABACAVIR and LAMIVUDINE tablets for oral suspension, for oral use (Abacavir and lamivudine tablets for oral suspension).

PI, Medication Guide and Warning Card: OPDP's comments on the proposed labeling are based on the draft PI, Medication Guide, and Warning Card received by electronic mail from DAVP (Monica Zeballos) on July 11, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Monica Zeballos) on July 11, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov .

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WENDY R LUBARSKY
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LABEL, LABELING, AND USE-RELATED RISK ANALYSIS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 12, 2019
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 204311
Product Name and Strength:	Abacavir and Lamivudine Tablets, for Oral Suspension, 60 mg/30 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mylan Laboratories Limited
FDA Received Date:	October 28, 2014, February 6, 2019, April 18, 2019, May 15, 2019
OSE RCM #:	2019-312 and 2019-842
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Safety Evaluator for Human Factors:	James Schlick, MBA, RPh
DMEPA Team Leader (Acting):	Millie Shah, PharmD, BCPS
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg, we reviewed the proposed labels and labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY

On October 23, 2014, NDA 204311 was granted Tentative Approval under the provisions of the President's Emergency Plan for AIDS Relief (PEPFAR). On February 6, 2019, Mylan submitted a request for final approval of Abacavir and Lamivudine Tablets, for Oral Suspension, 60 mg/30 mg, for commercialization within the United States upon expiration of the pediatric exclusivity associated with U.S Patent No's 6,294,540, 6,641,843 and 6,004,968.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Response to Agency Information Request	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3.1 USE-RELATED RISK ANALYSIS

We requested the Sponsor submit a use-related risk analysis (URRA) for the product because the instructions require the user to suspend the tablet in water only. The sponsor submitted a URRA, which identified and evaluated the tasks involved in the use of the proposed product, the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors. The sponsor also provided information regarding known use-related problems with similar marketed products.

We reviewed the URRA for the proposed product and agree that the tasks included are comprehensive and appropriate for the proposed product. We also reviewed the URRA to ensure that all potential use errors and risks involved in using the proposed product, including known use issues with currently marketed products, have been considered and adequately mitigated. In addition, we did not identify any new, differing, or unique risks for the proposed product as compared to other approved oral tablet for suspension products intended for use by laypersons. We utilized the information from the URRA to inform our evaluation of the proposed labels and labeling for this product.

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted labels and labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Antiviral Products

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information (FPI)			
1.	The recommended dose in Section 2.2 *Recommended Dosage for Pediatric Patients* is listed as (b) (4) which could lead to confusion.	As currently listed, the recommended dose statement could be misinterpreted as (b) (4)	To provide clarity, we recommend revising the dosage statement to indicate, (b) (4)
2.	Table 1 includes the abbreviations (b) (4) which could lead to confusion.	Healthcare providers are likely more familiar with the 3-digit alpha-numeric abbreviations, ABC and 3TC, which are designated for abacavir and lamivudine, respectively.	To provide clarity, we recommend replacing the (b) (4) abbreviations for abacavir and lamivudine with each active ingredient's 3-digit alpha-numeric designated abbreviations "ABC" and "3TC," respectively.
3.	As currently presented, the recommended dosage information in Table 1 could lead to confusion or misinterpretation.	The table is difficult to read due to crowded text. Additionally, there is an inconsistent use of ½ vs .5 tablet(s) throughout the table.	To provide clarity, we recommend removing the mg dose information presented in the 2nd and 3rd columns of Table 1 (i.e., remove (b) (4), etc.). Below we provide suggested revisions for Table 1 (see example below).

Suggested Revision to Table 1:

Table 1. Dosing Recommendations for Abacavir and Lamivudine Tablets for Oral Suspension for Pediatric Patients 3 months of age and older

Weight (kg)	Dosage Regimen Using Scored Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg		Total Daily Dose (mg)
	AM Dose	PM Dose	
5 to less than 6 kg	½ tablet	1 tablet	90 mg ABC/45 mg 3TC
6 to less than 9 kg	1 tablet	1 tablet	120 mg ABC/60 mg 3TC
9 to less than 12 kg	1 ½ tablets	1 ½ tablets	180 mg ABC/90 mg 3TC
12 to less than 17 kg	2 tablets	2 tablets	240 mg ABC/120 mg 3TC
17 to less than 20 kg	2 ½ tablets	2 ½ tablets	300 mg ABC/150 mg 3TC
20 to less than 25 kg	3 tablets	3 tablets	360 mg ABC/180 mg 3TC
25 to less than 29 kg	3 ½ tablets	3 ½ tablets	420 mg ABC/210 mg 3TC
29 to less than 35 kg	4 tablets	4 tablets	480 mg ABC/240 mg 3TC
35 kg or greater	5 tablets	5 tablets	600 mg ABC/300 mg 3TC

ABC = abacavir; 3TC = lamivudine

4.	The Dosage and Administration section does not prominently convey that Abacavir and Lamivudine Tablets for Oral Suspension are not to be chewed.	Per the Information Request response received on April 18, 2019 (see Appendix F), Mylan clarified that Abacavir and Lamivudine Tablets for Oral Suspension are not recommended to be chewed. The tablets may be administered by	To provide clarity, we recommend including, the following statements in Section 2.2, above the *Method of Preparation* section. (b) (4)

		swallowing whole or by dispersing in water according to the preparation instructions.	Additionally, under the *Methods of Preparation* section, we recommend removing the the non-affirmative statement, "(b) (4) (b) (4)" In place of the previous statement, we recommend including the statement, "Do not chew," to occur as the last sentence of Step 2. We recommend the above recommendations be applied to the *Methods of Preparation* sections of the FPI and Medication Guide.
5.	The *Method of Preparation* section includes the statement, (b) (4)	(b) (4)	We recommend removing the statement from the FPI and Medication Guide.
Medication Guide			
6.	(b) (4)		

General Labeling Issues	
7.	We note that the container label and carton labeling includes an abacavir sulfate equivalency statement, which is not included in Section 3 of the full prescribing information (FPI). We defer to OPQ to determine the appropriateness of including an abacavir sulfate equivalency statement in Section 3 of the FPI and on the container label and carton labeling.
8.	We note the statement, "Dispense in original container" in the HOW SUPPLIED/STORAGE AND HANDLING section of the full prescribing information. We defer to OPQ to determine the appropriateness of this statement in the full prescribing information and whether the statement should be added to the container label/carton labeling. If there is not sufficient data to suggest that tablets must only be dispensed in the original container, then we recommend removal of this statement from labels and labeling.

Table 3: Identified Issues and Recommendations for Mylan Laboratories Limited (entire table to be conveyed to Applicant)

Container Label and Carton Labeling			
1.	A recommended dosage statement is missing.	21 CFR 201.55 requires labels of prescription drugs bear a statement of the recommended or usual dosage.	Include the statement, "Recommended Dosage: See Prescribing Information" on the container label and carton labeling.
2.	The Note to Authorized Dispensers information is located on the side panel of the container label.	In instances where the pharmacy removes the container from the carton prior to dispensing, this important information could be missed.	Consider moving the Note to Authorized Dispenser information to the principal display panel of the container label if room permits.

5 CONCLUSION

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Abacavir and Lamivudine received on April 18, 2019 from Mylan Laboratories Limited.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Abacavir and Lamivudine</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>Abacavir and Lamivudine</td></tr>
<tr><td>Indication</td><td>In combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dosage Form</td><td>Tablets, for Oral Suspension</td></tr>
<tr><td>Strength</td><td>60 mg/30 mg</td></tr>
<tr><td>Dose and Frequency</td><td>Recommended dose for pediatric patients 3 months and older: 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)

Table 1. Dosing Recommendations for Abacavir and Lamivudine Tablets for Oral Suspension Pediatric Patients
<table>
<tr><td rowspan="2">Weight (kg)</td><td colspan="2">Dosage Regimen Using Scored Abacavir and Lamivudine Tablets for Oral Suspension, 60 mg/30 mg</td><td rowspan="2">Total Daily Dose (mg)</td></tr>
<tr><td>AM Dose (mg)</td><td>PM Dose (mg)</td></tr>
<tr><td>5</td><td>½ tablet (30 mg A/15 mg L)</td><td>1 tablet (60 mg A/30 mg L)</td><td>90A/45L</td></tr>
<tr><td>6 - < 9</td><td>1 tablet (60 mg A/30 mg L)</td><td>1 tablet (60 mg A/30 mg L)</td><td>120A/60L</td></tr>
<tr><td>9 - < 12</td><td>1.5 tablets (90 mg A/45 mg L)</td><td>1.5 tablets (90 mg A/45 mg L)</td><td>180A/90L</td></tr>
<tr><td>12 - < 17</td><td>2 tablets (120 mg A/60 mg L)</td><td>2 tablets (120 mg A/60 mg L)</td><td>240A/120L</td></tr>
<tr><td>17 - < 20</td><td>2.5 tablets (150 mg A/75 mg L)</td><td>2.5 tablets (150 mg A/75 mg L)</td><td>300A/150L</td></tr>
<tr><td>20 - < 25</td><td>3 tablets (180 mg A/90 mg L)</td><td>3 tablets (180 mg A/90 mg L)</td><td>360A/180L</td></tr>
<tr><td>25 - < 29</td><td>3.5 tablets (210 mg A/105 mg L)</td><td>3.5 tablets (210 mg A/105 mg L)</td><td>420A/210L</td></tr>
<tr><td>29 - < 35</td><td>4 tablets (240 mg A/120 mg L)</td><td>4 tablets (240 mg A/120 mg L)</td><td>480A/240L</td></tr>
<tr><td>≥ 35</td><td>5 tablets (300 mg A/150 mg L)</td><td>5 tablets (300 mg A/150 mg L)</td><td>600A/300L</td></tr>
</table>
A= abacavir; L= lamivudine</td></tr>
</table>

	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. One teaspoon (5 mL) of drinking water should be used for ½ tablet. 2. Swirl the container (approximately 2-3 minutes) until the tablet(s) for oral suspension breaks up into pieces small enough for the child to swallow. Tablets should not be chewed. A spoon can be used to crush the pieces, if needed. 3. Drink the mixture within 1 hour. If not administered immediately upon preparation, swirl the container (approximately 2-3 minutes) before administration. Discard the mixture if not used within 1 hour. 4. Rinse the container with an additional small amount of water (approximately one to two teaspoons (5 mL to 10 mL) per tablet) and drink the contents to ensure that the entire dosage is taken. **Do not mix the abacavir and lamivudine tablets for oral suspension with any liquid other than water.** Split tablets when needed. Store unused half tablets in a separate bag or bottle and use as soon as practical.
How Supplied	Carton containing one bottle of 60 tablets; Each tablet is scored.
Storage	Store below 30°C (86°F). Dispense in original container.
Container Closure	Bottles with induction seal and child-resistant cap

APPENDIX F. RESPONSE TO AGENCY INFORMATION REQUEST

We requested the Sponsor submit a use-related risk analysis (URRA) for the product because the instructions require the user to suspend the tablet in water only.

We received a URRA from the Sponsor on May 15, 2019 and the URRA is accessible at:

\\CDSESUB1\evsprod\NDA204311\0024\m1\us\12-cover-letters\cover-letter-0024-information-request-response-20190515.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Abacavir and Lamivudine labels and labeling submitted by Mylan Laboratories Limited.

- Container label received on October 28, 2014, as referenced in the February 6, 2019 submission
- Carton labeling received on April 18, 2019
- Warning Card received on February 6, 2019
- Prescribing Information and Medication Guide (Images not shown) received on April 18, 2019, available at: \\cdsesub1\evsprod\nda204311\0022\m1\us\114-labeling\draft\labeling\draft-labeling-text-clean.pdf

G.2 Label and Labeling Images

- Container label

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

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

IRENE Z CHAN on behalf of VALERIE S WILSON
07/12/2019 01:03:41 PM

MILLIE B SHAH
07/12/2019 01:50:54 PM

JAMES H SCHLICK
07/12/2019 01:56:09 PM

IRENE Z CHAN
07/12/2019 02:01:45 PM

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: October 3, 2014

TO: Wayne Dehaven, Ph.D.
Director (Acting)
Division of Bioequivalence I
Office of Generic Drugs

Debra Birnkrant, M.D.
Director
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products

FROM: Chase H. Bourke, Ph.D.
GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief (Acting), GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NON-RESPONSIVE
NDA 204-311, and NON-RESPONSIVE sponsored by Mylan Laboratories

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Table of Contents

1. Summary

At the request of the Divisions of Bioequivalence I (DBE), Office of Generic Drugs (OGD) and the Division of Antiviral Products (DAVP), Office of Antimicrobial Products (OAP), the Division of Bioequivalence and GLP Compliance (DBGLPC) inspected the analytical portion of the requested studies utilizing a bioequivalence surveillance approach. A summary of the inspected studies is provided below.

Review Div.	Application	Studies	Drug Product	Recommendation
DBI	NON-RESPONSIVE			
DBI				
DAVP	NDA 204-311	BA12101519-01 and BA12101520-01	Abacavir sulfate and Lamivudine tablets, 60 mg/30 mg	Acceptable
DAVP	NON-RESPONSIVE			

The FDA inspectors audited the following studies at Mylan Laboratories, Hyderabad, India:

Division of Bioequivalence I (OGD)

NON-RESPONSIVE

NON-RESPONSIVE

Division of Anti-Viral Products (DAVP)
NDA 204-311 (Abacavir sulfate and Lamivudine tablets)

BA12101519-01:" An open label, randomized, three-period, three-treatment, three-sequence, crossover, balanced, single dose oral bioequivalence study of test product abacavir sulfate/lamivudine dispersible tablets 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) of ViiV Healthcare, Research Triangle Park, USA in healthy adult human subjects under fasting conditions"

BA12101520-01:" An open label, randomized, three-period, three-treatment, three-sequence, crossover, balanced, single dose oral bioequivalence study of test product abacavir sulfate/lamivudine dispersible tablets 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) of ViiV Healthcare, Research Triangle Park, USA in healthy adult human subjects under fed conditions"

NON-RESPONSIVE

The FDA inspectors covered both the clinical and analytical portions from the above studies. The selection of studies for this BE surveillance inspection was based on pre-set, risk-based criteria.

2. Recommendation

The analytical data from the inspected studies are acceptable for review.

3. Inspectional Findings

The inspection was completed by Chase H. Bourke, Ph.D (OSI) and Gene Arcy (ORA, LOS-DO) at **Mylan Laboratories, Hyderabad, India** (August 4-14, 2014).

The audits included a thorough examination of facilities and equipment, reviews of study records, including correspondence, and interviews and discussions with Mylan's management and staff. As part of global assessment of the firm's bioanalytical operations, several key study components that best represent the firm's bioanalytical operations were selected and audited across the studies. DBGLPC audited the eight studies requested for audit by OGD and DAVP using a surveillance approach.

NON-RESPONSIVE

4. Final Site Classification

NAI – Mylan Laboratories, Inc, Hyderabad, India
FEI: 3006355432

cc:
OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Dasgupta/Skelly/Bourke
OSI/DBGLPC/Fenty-Stewart/Nkah/Dejernett/Johnson
OPS/OGD/DBEI/Dehaven/Wong/Yoon
OND/OAP/DAVP/Birnkrant/Zeballos/Murray
ORA/LOS-DO/Arcy

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Inspections/BE Program/Analytical sites/Mylan Laboratories, Hyderabad, India

Draft: CHB 09/26/2014
Edits: AD 10/03/2014; CRB 10/3/2014

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5. Attachments

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/s/

CHASE H BOURKE
10/03/2014

CHARLES R BONAPACE
10/03/2014

WILLIAM H TAYLOR
10/03/2014

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: October 3, 2014

TO: Debra Birnkrant, M.D.
Director
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products

FROM: Chase Bourke, Ph.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Acting Chief, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 204-311, Abacavir sulfate and Lamivudine tablets, 60 mg/30 mg, sponsored by Mylan Pharmaceuticals Inc., Morgantown, WV

At the request of the Division of Antiviral Products (DAVP), the Division of Bioequivalence and GLP Compliance (DBGLPC) arranged an inspection of the clinical portion of the following bioequivalence studies:

BA12101519-01:" An open label, randomized, three-period, three-treatment, three-sequence, crossover, balanced, single dose oral bioequivalence study of test product abacavir sulfate/lamivudine dispersible tablets 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) of ViiV Healthcare, Research Triangle Park, USA in healthy adult human subjects under fasting conditions"

BA12101520-01:" An open label, randomized, three-period, three-treatment, three-sequence, crossover, balanced, single dose oral bioequivalence study of test product abacavir sulfate/lamivudine dispersible tablets 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) of ViiV Healthcare, Research Triangle Park, USA in healthy adult human subjects under fed conditions"

The clinical portion of both studies was audited at **Cliantha Research Limited, 1st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara, India** by ORA investigator Gene Arcy (ORA LOS-DO) between August 18-22, 2014.

The audit included a thorough examination of study records, including communications between Cliantha and the sponsor, facilities and equipment, and interviews and discussions with Cliantha's management and staff.

Following the inspection at Cliantha Research Limited, no objectionable conditions were observed and no form 483 was issued.

Conclusions:

Following the above inspection, the data from the clinical portion of studies BA12101519-01 and BA12101520-01 were found to be reliable. Therefore, I recommend that the data be accepted for agency review.

Chase H. Bourke, Ph.D.
GLP Branch, DBGLPC, OSI

Final Classification:

NAI – Cliantha Research Ltd, Vadodara, India
FEI: 3007078964

CC:
OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Dasgupta/Skelly/Bourke
OSI/DBGLPC/Fenty-Stewart/Nkah/Dejernett/Johnson
OND/OAP/DAVP/Birnkrant/Zeballos/Murray
ORA/LOS-DO/Arcy

Draft: CHB 9/26/2014
Edit: AD 10/02/2014
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Inspections/BE Program/Clinical sites/Cliantha Research, Vadodara, India
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FACTS: 8751728

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/s/

CHASE H BOURKE
10/03/2014

CHARLES R BONAPACE
10/03/2014

WILLIAM H TAYLOR
10/03/2014