# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214439Orig1s000

# OTHER REVIEW(S)

# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

| | |
|---|---|
| Date of This Memorandum: | February 7, 2022 |
| Requesting Office or Division: | Division of Cardiology and Nephrology (DCN) |
| Application Type and Number: | NDA 214439 |
| Product Name and Strength: | Norliqva (amlodipine) oral solution, 1 mg/mL |
| Applicant/Sponsor Name: | CMP Pharma, Inc. |
| OSE RCM #: | 2020-1308-2 |
| DMEPA Team Leader: | Hina Mehta, PharmD |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on January 6, 2022 for Norliqva (amlodipine) oral solution. We reviewed the revised container label for Norliqva (amlodipine) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations from the Office of Pharmaceutical Quality to update the equivalency statement.

## 2 CONCLUSION

The revised container label is acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JANUARY 6, 2022

Container labels

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HINA S MEHTA
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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: | December 27, 2021 |
| Requesting Office or Division: | Division of Cardiology and Nephrology (DCN) |
| Application Type and Number: | NDA 214439 |
| Product Name, Dosage Form, and Strength: | Norliqva (amlodipine) oral solution, 1 mg/mL |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | CMP Development, LLC |
| FDA Received Date: | March 5, 2021 and August 25, 2021 |
| OSE RCM #: | 2020-1308-1 |
| DMEPA 2 Safety Evaluator: | Celeste Karpow, PharmD, MPH |
| DMEPA 2 Team Leader: | Hina Mehta, PharmD |

# 1 REASON FOR REVIEW

CMP Development, LLC (CMP) submitted a Class 2 resubmission for Norliqva (amlodipine), NDA 214439 on August 25, 2021 following issuance of a complete response from the Agency on April 22, 2021. The most recent labels and labeling were submitted as an amendment to the application on March 5, 2021. As part of the approval process for Norliqva (amlodipine) oral solution, this review evaluates the proposed container label and prescribing information for areas of vulnerability that may lead to medication errors.

## 1.1 BACKGROUND

CMP submitted a 505(b)(2) NDA to obtain marketing approval for Norliqva (amlodipine) oral solution. The listed drug (LD) for this product is Norvasc (amlodipine besylate) tablets. Norliqva is proposed for the same indications as Norvasc which includes hypertension and coronary artery disease.

Norvasc is currently available as 2.5 mg, 5 mg, and 10 mg tablets. We note the proposed amlodipine oral solution has the same dosage regimen (5 mg once daily with a maximum dose of 10 mg once daily and 2.5 mg once daily initial dose for small, fragile, elderly patients or patients with hepatic insufficiency in addition to pediatrics), route, and indication as Norvasc.

## 1.2 REGULATORY HISTORY

NDA 214439 was originally submitted on June 22, 2020; however, the application received a Complete Response (CR) letter on April 22, 2021 due to facility inspections and product quality issues. The CR letter explained that FDA reserved comment on the proposed labeling until the application is otherwise adequate. CMP then submitted a Class 2 resubmission on August 25, 2021.

We previously reviewed the labels and labeling[a].

# 2 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 Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Human Factors Study | C – N/A |
| ISMP Newsletters* | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |

[a] Aidoo, M. Label and Labeling Review for Norliqva (NDA 214439). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 24. RCM No.: 2020-1308.

| Table 1. Materials Considered for this Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed strength of 1 mg/mL for Norliqva oral solution is already established for an existing compounded Amlodipine oral liquids (AmLODIPine Bes+SyrSpend SF from Fagron[b]), and the USP monograph for amlodipine compounded oral suspension [100 mg/100 mL (1 mg/mL)][c]. In addition, the dosage regimen proposed for Norliqva is the same as the approved dosage regimen for the listed drug, Norvasc.

We performed a risk assessment of the full prescribing information (PI) and container label to identify deficiencies that may lead to medication errors and areas for improvement. Our review of the PI identified areas where the label and labeling may be improved to promote the safe use of the product. Thus, we provide related recommendations below in Section 4.1. We find the container label acceptable.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI for amlodipine oral solution may be improved to promote the safe use of the product. We provide recommendations in Sections 4.1 for the Division. The Applicant implemented all of our recommendations for the container label and we have no additional recommendations at this time.

[b] https://shop.fagron.us/en-us/product/wci00167/syrspend-c2-ae-sf-ph4-convenience-p.aspx

[c] Amlodipine compounded oral suspension USP monograph. Accessed February 13, 2019 at: https://online.uspnf.com/uspnf/document/GUID-26ACA8DE-9192-4B6F-BCF2-0C79124344A5_1_en-US?highlight=amlodipine.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration Section

a. As currently presented, the route of administration is missing. We recommend adding the route of administration, 'oral' to the dosing information. For example, consider the following revisions:

i. "Adult recommended starting dose: 5 mg orally once daily with a maximum of 10 mg orally once daily."

ii. "Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg orally once daily…"

iii. "Pediatric starting dose: 2.5 mg to 5 mg orally once daily."

B. Prescribing Information (Full)

1. Dosage and Administration Section

a. As currently presented, the route of administration is missing. We recommend adding the route of administration, 'oral' to the dosing information in Section 2.1 and 2.2.

b. We recommend revising the dose range for treatment of Angina and Coronary artery disease to include the units of measure for the 5 mg dose as well as the frequency of administration, as follows:

*i.* *"Angina:* The recommended dose for chronic stable and vasospastic angina is 5 mg to 10 mg orally once daily,… Most patients will require 10 mg orally once daily for adequate effect."

*ii.* *"Coronary artery disease*: The recommended dose range for patients with coronary artery disease is 5 mg to 10 mg orally once daily.

2. How Supplied/Storage and Handling Section

a. We recommend adding the color (e.g., pale straw colored solution per description in Section 3) and taste of the oral solution to Section 16 to facilitate identification of the oral solution.

b. We note the statement "Dispense to patients in original packaging" is on the container label. As such, we recommend adding the statement "Store and dispense in original packaging" after the storage statement to ensure this important information is not missed.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Norliqva received on March 5, 2021 from CMP Development, LLC, and the listed drug (LD).

| Table 2. Relevant Product Information for Norliqva and the Listed Drug | | |
|---|---|---|
| Product Name | Norliqva | Norvasc [d] |
| Initial Approval Date | N/A | July 31, 1992 |
| Active Ingredient | amlodipine | |
| Indication | Calcium channel blocker and may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of:<br><br>• Hypertension<br>o Indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.<br>• Coronary Artery Disease<br>o Chronic Stable Angina<br>o Vasospastic Angina (Prinzmetal's or Variant Angina)<br>o Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40% | |
| Route of Administration | oral | |
| Dosage Form | oral solution | tablets |
| Strength | 1 mg/mL | 2.5 mg, 5 mg, and 10 mg |
| Dose and Frequency | - Adult recommended starting dose: 5 mg once daily with maximum dose 10 mg once daily.<br>o Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily. This dose may also be used when adding amlodipine to other antihypertensive therapy.<br>- Pediatric starting dose (6 to 17 years of age): 2.5 mg to 5 mg once daily.<br>* Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, | |

[d] Norvasc [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Oct 2017. [cited 2021 DEC 15.] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019787s062lbl.pdf. w

| | | |
|---|---|---|
| | However, if clinically warranted, provided the patient is assessed frequently. | |
| How Supplied | 150 mL amber glass bottle | -2.5 mg tablet: Bottle of 90<br>-5 mg tablet: Bottles of 90 and 300, unit dose package of 100<br>-10 mg tablet:<br>Bottle of 90 and unit dose package of 100 |
| Storage | Store at 20°C to 25°C (68 to 77°F); excursion permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. | Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant containers (USP). |
| Container Closure | Glass bottle with a child-resistant closure | Bottle and unit dose package |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 15, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'amlodipine'. Our search identified two previous reviews[e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[e] Thomas, S. Label and Labeling Review for Amlodipine (NDA 211340). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 28. RCM No.: 2018-2140.

[f] Aidoo, M. Label and Labeling Review for Norliqva (NDA 214439). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 24. RCM No.: 2020-1308.

## 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,[g] along with postmarket medication error data, we reviewed the following Norliqva labels and labeling submitted by CMP Development, LLC.

- Container label received on March 5, 2021
- Prescribing Information (Image not shown) received on March 5, 2021, available from \\CDSESUB1\evsprod\nda214439\0010\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi.doc

### G.2 Label and Labeling Images

Container Label


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

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

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DATE: May 27, 2021

TO: Norman Stockbridge, M.D.
Director
Division of Cardiology and Nephrology
Office of New Drugs

Nick Kozauer, M.D.
Director (Acting)
Division of Neurology II
Office of New Drugs

Partha Roy, Ph.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Kara Scheibner, Ph.D.
DGDSI
OSIS

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Remote Record Review (RRR) of (b) (4) (b) (4)

## 1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a Remote Record Review (RRR) of the analytical portion of studies Non-Responsive Non-Responsive, study 19-029 (NDA 214439, amlodipine) and studies Non-Responsive conducted at (b) (4).

We observed objectionable findings that impact the reliability of some study data.

## 1.1. Recommendation

Based on our review of the RRR observations and the firm's response, we conclude the RRR observations impact the reliability of data from the audited study NON-RESPONSIVE NON-RESPONSIVE However, the objectionable conditions were isolated in nature and did not impact the reliability of all studies. Therefore, the data from NON-RESPONSIVE, 19-029 (NDA 214439), NON-RESPONSIVE are reliable.

## 2. Reviewed Studies

NON-RESPONSIVE

NON-RESPONSIVE

**Study 19-029 (NDA 214439)**
"An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Amlodipine 1 mg/mL Oral Solution (Dose: 10 mL equivalent to the dose of 10 mg of amlodipine) of CMP Development LLC, USA with NORVASC® (amlodipine besylate) 10 mg (equivalent to 10 mg of amlodipine) Tablets, Marketing Authorization holder: Pfizer Labs (Division of Pfizer Inc., NY), NY 10017 in healthy, adult, human subjects under fasting conditions"
Sample Analysis Period: (b) (4)

NON-RESPONSIVE

**3. Scope of RRR**

OSIS scientists Melkamu Getie-Kebtie, Ph.D., R.Ph. and Kara Scheibner, Ph.D. reviewed the analytical portion of the above studies conducted at (b) (4) from (b) (4).

The RRR included an examination of study records, method validation, and sample analysis, and interviews with the firm's management and staff.

**4. RRR Observations**

At the conclusion of the RRR, we observed objectionable conditions that impact reliability of some study data. We discussed the following items with the firm's management during the RRR close-out meeting.

(b) (4)

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(b) (4)

**5. Conclusion**

We conclude that some of the data NON-RESPONSIVE are not reliable. NON-RESPONSIVE

NON-RESPONSIVE

However, the data from studies NON-RESPONSIVE, 19-029 (NDA 214439), NON-RESPONSIVE are reliable.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Lewin/Skelly/Au/Scheibner/Getie-Kebtie

Draft: MG 5/13/2021, 5/19/2021, 5/25/2021, 5/26/2021, 5/27/2021;
KAS 5/7/2021, 5/24/2021, 5/25/2021, 5/26/2021

Edit: SA 05/14/2021, 5/24/2021, 5/25/2021, 5/26/21, 5/27/21; JC 05/25/2021, 5/26/21, 5/27/21

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ (b) (4) (b) (4) /RRR (b) (4)

OSIS File #: BE NON-RESPONSIVE 8969 (NDA 214439), NON-RESPONSIVE

**Attachments**

1. Response to US FDA remote record review observations
2. QUANT Method
3. Logbook for storage and retrieval working standards/reference standards
4. Logbook for balance
5. Calculation and preparation of fresh calibration curve standard and quality control samples

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STANLEY AU
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Team Lead

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

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DATE: April 20, 2021

TO: Norman Stockbridge, M.D.
Director
Division of Cardiology and Nephrology
Office of New Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Kara Scheibner, Ph.D.
DGDSI
OSIS

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Response to consult-NDA 214439: (b) (4) (b) (4)

## 1. Consult Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a Remote Record Review (RRR) at (b) (4) (b) (4). This document discusses the findings relevant to the analytical portion of study 19-029 (NDA 214439, amlodipine) that was evaluated as part of the RRR. **Additional studies from other applications that were also covered during RRR will not be discussed in this document.**

We observed objectionable findings during the RRR relevant to NDA 214439.

### 1.1. Recommendation

Based on conversations with the firm's management and information provided during the RRR regarding our findings, we conclude observations 1 and 2 listed in section 3 of this memo do not have impact on data reliability for study 19-029. The impact of observation 3 will be assessed once the firm's written

response is received. However, currently there is no evidence indicating the finding affects the data reliability of study 19-029.

**2. Reviewed Study under NDA 214439**

**Study 19-029**
"An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Amlodipine 1 mg/mL Oral Solution (Dose: 10 mL equivalent to the dose of 10 mg of amlodipine) of CMP Development LLC, USA with NORVASC® (amlodipine besylate) 10 mg (equivalent to 10 mg of amlodipine) Tablets, Marketing Authorization holder: Pfizer Labs (Division of Pfizer Inc., NY), NY 10017 in healthy, adult, human subjects under fasting conditions"
Sample Analysis Period: (b) (4)

**3. Consult Findings**

We observed the following objectionable findings pertinent to study 19-029 and its method validation. The firm intends to provide written responses to these findings by 4/30/2021. OSIS's recommendations below are based on conversations with the firm's staff and information provided during the RRR. Review of the firm's response, once received, will be incorporated into the RRR memo for the (b) (4) site that is currently pending.

(b) (4)

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(b) (4)

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Skelly/Au/Lewin/Getie-Kebtie/Scheibner

Draft: MG 4/15/2021, 4/16/2021, 4/19/2021, 4/20/2021
Edit: SA 4/15/2021; 04/16/2021, 4/19/2021; JC 4/16/2021, 4/19/2021

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/[redacted]/RRR[redacted]

OSIS File #: BE 8969

**Attachments**

1. Global P&A statistics_MV-109-01
2. Global P&A statistics_MV-109-01 (ADD 5)

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Team Lead

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DATE: 3/31/2021

TO: Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214439

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

## Rationale

The Office of Regulatory Affairs (ORA) inspected the site in February 2020, which falls within the surveillance interval. The inspection was conducted under the following submission: NON-RESPONSIVE

The final classification for the inspection was No Action Indicated (NAI).

OSIS notes that pharmacokinetic anamolies were identified for BE studies conducted at the site in 2018 and 2019. However, based on the nature of the issues identified, the utility of an inspection of the site is unclear and the site is being monitored for future action.

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

| Facility Type | Facility Name | Facility Address |
|---|---|---|
| Clinical | Synapse Labs | Majestic Plaza, S. No. 21/5, Kharadi-Mundhwa Bypass, Kharadi, Pune, Maharashtra, India |

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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: | March 24, 2021 |
| To: | Sabry Soukehal<br>Senior Regulatory Health Project Manager<br>**Division of Cardiology and Nephrology (DCN)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| | Sharon R. Mills, BSN, RN, CCRP<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Jessica Chung, PharmD, MS<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)** |
| | Zarna Patel, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Patient Package Insert (PPI) |
| Drug Name (established name): | NORLIQVA (amlodipine (b) (4) |
| Dosage Form and Route: | oral solution |
| Application Type/Number: | NDA 214439 |
| Applicant: | CMP Development LLC |

# 1 INTRODUCTION

On June 22, 2020, CMP Development LLC submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 214439 for NORLIQVA (amlodipine (b) (4)), oral solution. This submission relies on the Reference Listed Drug (RLD) NORVASC (amlodipine besylate) under NDA 019787. The proposed indications for NORLIQVA (amlodipine (b) (4)), oral solution are for use alone or in combination with other antihypertensive and antianginal agents for the treatment of:

Hypertension

- For the treatment of hypertension, to lower blood pressure

Coronary Artery Disease

- For the symptomatic treatment of chronic stable angina
- For the treatment of confirmed or suspected vasospastic angina
- Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%

The proprietary name NORLIQVA was determined to be conditionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) on January 8, 2021.

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 Cardiology and Nephrology (DCN)) on August 18, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for NORLIQVA (amlodipine (b) (4)), oral solution.

# 2 MATERIAL REVIEWED

- Draft NORLIQVA (amlodipine (b) (4)), oral solution PPI received on June 22, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 12, 2021.
- Draft NORLIQVA (amlodipine (b) (4)), oral solution Prescribing Information (PI) received on June 22, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 12, 2021.

# 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ 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 PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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

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

## Memorandum

**Date:** March 19, 2021

**To:** Sabry Soukehal, Senior Regulatory Health Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

**From:** Zarna Patel, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** James Dvorsky, PharmD, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for NORLIQVA® (amlodipine (b) (4)), oral solution

**NDA**: 214439

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In response to DCN consult request dated August 18, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for NORLIQVA® (amlodipine (b) (4)), oral solution.

**Labeling**: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN (Sabry Soukehal) on March 12, 2021 and have no additional comments at this time.

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

**Carton and Container Labeling**: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 5, 2021, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796- 3822 or zarna.patel@fda.hhs.gov.

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

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ZARNA PATEL
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LABEL AND LABELING 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: | February 24, 2021 |
| Requesting Office or Division: | Division of Cardiology and Nephrology (DCN) |
| Application Type and Number: | NDA 214439 |
| Product Name, Dosage Form, and Strength: | Norliqva (amlodipine (b) (4)) oral solution, 1 mg/mL |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | CMP Development LLC (CMP) |
| FDA Received Date: | June 22, 2020 |
| OSE RCM #: | 2020-1308 |
| DMEPA Safety Evaluator: | Mariette Aidoo, PharmD, MPH |
| DMEPA Team Leader: | Hina Mehta, PharmD |

## 1 REASON FOR REVIEW

As a part of the NDA review process, this review evaluates the proposed Norliqva (amlodipine (b) (4)) oral solution container label and prescribing information (PI) for areas of vulnerability that could lead to medication errors.

## 2 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 Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Human Factors Study | C – N/A |
| ISMP Newsletters* | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

CMP submitted a 505(b)(2) NDA to obtain marketing approval for Norliqva (amlodipine (b) (4) oral solution. The listed drug (LD) for this product is Norvasc (amlodipine besylate) tablets. Norvasc is currently available as 2.5 mg, 5 mg, and 10 mg tablets. We note that the proposed amlodipine (b) (4) oral solution has the same dosage regimen (5 mg once daily with a maximum dose of 10 mg once daily and 2.5 mg once daily initial dose for small, fragile, elderly patients or patients with hepatic insufficiency in addition to pediatrics), route, and indication as the LD.

CMP is proposing the amlodipine (b) (4) oral solution with a proposed strength of 1 mg/mL in a 150 mL bottle. We note this amlodipine concentration has already been established via existing compounded Amlodipine oral liquids (AmLODIPine Bes+SyrSpend SF from Fagron[a]), and the USP monograph for amlodipine compounded oral suspension [100 mg/100 mL (1 mg/mL)][b].

[a] https://shop.fagron.us/en-us/product/wci00167/syrspend-c2-ae-sf-ph4-convenience-p.aspx

We performed a risk assessment of the full prescribing information (PI) and container labels to identify deficiencies that may lead to medication errors and areas for improvement. Our review of the container label and prescribing information (PI) identified areas where the label and labeling may be improved to promote the safe use of the product. Thus, we provide related recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label and PI for amlodipine oral solution may be improved to promote the safe use of the product. We provide recommendations in Sections 4.1 for the Division and in Section 4.2 for the Applicant.

### 4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. We recommend replacing all instances of the proprietary name with the conditionally acceptable proprietary name 'Norliqva'.
2. Dosage and Administration Section
    a. We recommend adding the route (i.e. orally) to the dosing information as currently presented the route of administration is missing. Revise as follows:
        i. "Adult recommended starting dose: 5 mg orally once daily with a maximum of 10 mg orally once daily."
        ii. "Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg orally once daily."
        iii. "Pediatric starting dose: 2.5 mg to 5 mg orally once daily.".

B. Prescribing Information (Full)

1. Dosage and Administration Section
    a. We recommend adding the route (i.e. orally) to the dosing information as currently presented the route of administration is missing in Section 2.1 and 2.2.
    b. We recommend revising the following dose range provided for treatment of Angina and Coronary artery disease to include the units of measure for the 5 mg dose as well as the frequency of administration, as follows:

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[b] Amlodipine compounded oral suspension USP monograph. Accessed February 13, 2019 at: https://online.uspnf.com/uspnf/document/GUID-26ACA8DE-9192-4B6F-BCF2-0C79124344A5_1_en-US?highlight=amlodipine.

*i.* *"Angina:* The recommended dose for chronic stable and vasospastic angina is 5 mg to 10 mg orally once daily,... Most patients will require 10 mg orally once daily for adequate effect."

*ii.* *"Coronary artery disease*: The recommended dose range for patients with coronary artery disease is 5 mg to 10 mg orally once daily.

2. How Supplied/Storage and Handling Section
    a. We recommend adding the color (e.g., pale straw colored solution per description in Section 3) and taste of the oral solution to Section 16 to facilitate identification of the oral solution.
    b. We recommend revising the storage statement for consistency as currently it is presented with "to" and "-" and degree symbol is missing for one of the numbers. Revise to "Store at 20°C to 25°C (68°F to 77°F); excursion permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."

(b) (4)

4.2 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC (CMP)

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels
    1. We note the proposed proprietary name, "Norliqva" was found conditionally acceptable as communicated in the Proprietary Name letter dated January 08, 2021. Therefore, we recommend replacing the proprietary name, (b) (4) with the conditionally acceptable name "Norliqva".
    2. As currently presented the placement of the graphic in front of the first letter "N" in the proprietary name is prominent. Placement of the graphic in front of the first letter in the proprietary name competes with readability of the proprietary name, which may lead to misinterpretation of the proprietary name as (b) (4). We recommend moving or decreasing the prominence of the graphic in front of the proprietary name as it may lead to misinterpretation of the proprietary name.

3. As currently presented the strength statement lacks prominence and uses the same font color (blue) used for several important statement on the container label. We recommend increasing the prominence of the strength statement.
4. The Rx Only statement appears prominent in large bold font. Decrease the prominence by debolding and reducing the font for the Rx Only statement.
5. To ensure consistency with the terminology in the Prescribing Information, revise the recommended dosage statement from (b) (4) to the following: "Recommended Dosage: See Prescribing Information."
6. As currently presented the dosage form (i.e. oral solution) is placed inside the parenthesis with the established name. For consistency with the change in the Prescribing Information we recommend revising the placement of the dosage form to outside the parenthesis.
7. As currently presented, there is a hyphen (-) in between the temperatures. Revise the storage information to read: Store at "20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). [See USP for controlled room temperature.]" for consistency with the Prescribing Information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Amlodipine received on June 22, 2020 from CMP Development LLC (CMP).

| Table 2. Relevant Product Information for Norliqva and the Listed Drug | | |
|---|---|---|
| Product Name | Norliqva | Norvasc[c] NDA 019787 |
| Initial Approval Date | N/A | July 31, 1992 |
| Active Ingredient | (amlodipine besylate) | Amlodipine besylate |
| Indication | Calcium channel blocker and may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of:<br><br>• Hypertension<br>o Indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.<br>• Coronary Artery Disease<br>o Chronic Stable Angina<br>o Vasospastic Angina (Prinzmetal's or Variant Angina)<br>o Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40% | |
| Route of Administration | Oral | |
| Dosage Form | Oral Solution | Tablets |
| Strength | 1 mg/mL | 2.5 mg, 5 mg, and 10 mg |
| Dose and Frequency | -Adult recommended starting dose: 5 mg once daily with maximum dose 10 mg once daily.<br>o Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily. This dose may also be used when adding amlodipine to other antihypertensive therapy.<br>-Pediatric starting dose (6 to 17 years of age): 2.5 mg to 5 mg once daily.<br>* Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrate more rapidly,<br>however, if clinically warranted, provided the patient is assessed frequently. | |

[c] Norvasc (amlodipine besylate) [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 OCT 8. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

| | | |
|---|---|---|
| How Supplied | 150 mL amber glass bottle | -2.5 mg tablet: Bottle of 90<br>-5 mg tablet: Bottles of 90 and 300, unit dose package of 100<br>-10 mg tablet:<br>Bottle of 90 and unit dose package of 100 |
| Storage | Store at 20°C -25°C (68-77°F); excursion permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. | Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant containers (USP). |
| Container Closure | Glass bottle with a child-resistant closure | Bottle and unit dose package |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 8, 2020, we searched for previous DMEPA reviews relevant to this current review using the term amlodipine. Our search identified one previous reviews[d] and we considered our previous recommendations to see if they are applicable for this current review.

[d] Thomas, S. Label and Labeling Review for Amlodipine (NDA 211340). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 28. RCM No.: 2018-2140.

## 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,[e] along with postmarket medication error data, we reviewed the following amlodipine labels and labeling submitted by CMP Development LLC (CMP).

- Container label received on June 22, 2020
- Carton labeling received on June 22, 2020
- Prescribing Information (Image not shown) received on June 22, 2020, available from \\cdsesub1\evsprod\nda214439\0000\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi.pdf

### G.2 Label and Labeling Images

(b) (4)

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

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