APPLICATION NUMBER:

211340Orig1s000

OTHER REVIEW(S)
I. GENERAL INFORMATION

NDA: 211340
Drug: KATERZIA (amlodipine benzoate) oral suspension 1 mg/mL
Class: Calcium channel blocker
Applicant: Silvergate Pharmaceuticals, Inc.
Approved indication: Treatment of hypertension in adults and children 6 years and older, to lower blood pressure and coronary artery disease [Chronic Stable Angina, Vasospastic Angina (Prinzmetal’s or Variant Angina) and Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40%]

II. REVIEW TEAM

Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
Division Director: Norman Stockbridge
Deputy Director: Aliza Thompson
Deputy Director for Safety: Mary Ross Southworth
Associate Director for Labeling: Michael Monteleone
Pediatric Medical Officer: Shetarra Walker
Pharmacology & Toxicology: Elizabeth Hausner
Safety Regulatory Project Manager: Lori Wachter
Regulatory Health Project Manager: Sabry Soukehal

Office of Clinical Pharmacology
Cross-Discipline Team Leader: Sudharshan Harihara
Reviewer: Anusha Ande

Office of Pharmaceutical Quality
Application Technical Lead: Mohan Sapru
Drug Substance: Monica Cooper
Drug Product: Stephanie Emory
Process and Facility: Mark Johnson
Microbiology: Denise Miller, Jason God
Biopharmaceutics: Kaushalkumar Dave, Jing Li

Office of Surveillance and Epidemiology
Division of Medication Error Prevention and Analysis: Sarah Thomas, Alice Tu
Division of Pharmacovigilance: Mihaela Jason
Office of Prescription Drug Promotion  
Zarna Patel  

III. BACKGROUND  

Amlodipine is a dihydropyridine calcium antagonist that inhibits calcium ion influx across the vascular smooth muscle and cardiac muscle cells causing vasodilation and a reduction in peripheral vascular resistance.  

Amlodipine besylate tablets at 2.5 mg, 5 mg, or 10 mg for oral administration have been marketed in the United States since 1992 under the brand name NORVASC® (Pfizer, Inc., NDA 19787) for the treatment of hypertension and coronary artery disease (chronic stable angina, vasospastic angina, and angiographically documented coronary artery disease).  

According to Silvergate Pharmaceuticals, Inc. (the Applicant), a ready-to-use amlodipine oral suspension at 1 mg/mL was developed to eliminate the need for extemporaneous compounding of tablets into a suspension to treat patients who have difficulty swallowing tablets. The sought indication is the treatment of hypertension in adults and children 6 years of age and older, to lower blood pressure; to reduce the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions; and for the treatment of coronary artery disease: chronic stable angina, vasospastic angina (Prinzmetal’s or variant angina), and angiographically documented coronary artery disease in patients without heart failure or an ejection fraction of < 40%.  

To seek approval of this oral suspension, the Applicant submitted a marketing application under the provisions of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (NDA 211340) that relies on the Agency’s previous finding of safety and effectiveness as well as the nonclinical safety data for NORVASC®, the reference listed drug. The Applicant also relies on published literature and the results of studies SG05-01 and SG05-02 described as follows:  

Study SG05-01: A Pilot, Open-Label, Randomized, Single-Dose, Two-Way Crossover Study to Determine the Relative Bioavailability of 5 mg Amlodipine Besylate Oral Suspension versus NORVASC® 5 mg Tablets Under Fasted Conditions in Healthy Adults.  

Study SG05-02: A Randomized, Single-Dose, Three-Way Crossover, Bioavailability Study of 5 mg Amlodipine Besylate Oral Suspension under Fasted and Fed Conditions and 5 mg NORVASC® Tablet under Fasted Conditions in Healthy Adults.  

Typical regulatory meetings were not held between the Applicant and the Division. On September 13, 2012 the Applicant submitted a meeting request to discuss the development plans of several drug products including amlodipine oral solution. The meeting was subsequently cancelled by the Applicant after receiving the Division’s preliminary comments.  

IV. APPLICATION REVIEW  

1. Regulatory Timeline  

Special Protocol Agreement: N/A  
Pre-NDA meetings: N/A  
NDA receipt date: September 14, 2018  
Filing date: November 13, 2018
Mid-cycle communication meeting: N/A
Late-cycle meeting: N/A
Advisory Committee: N/A
PDUFA goal date: July 14, 2019

2. **User Fee**

The user fee for this application was paid on September 12, 2018.

3. **Advisory Committee**

There was no Advisory Committee meeting for this NDA because the application did not raise significant issues regarding the safety or effectiveness of the drug.

4. **Pediatric Review**

At the time of NDA submission, the Applicant submitted a request for:
- A full waiver for coronary artery disease in the pediatric population from birth to 16 years of age. According to the Applicant, the incidence of this disease is very low and the necessary studies would be impossible or highly impractical due to the small number of patients who would be geographically dispersed. Hypertension pending results of the non-clinical toxicity requested by the Agency.

The Division agreed with the full waiver of pediatric studies for the coronary artery disease indication for the reasons cited by the Applicant.

In the Agreed iPSP, the Division had agreed to waiver of pediatric studies for hypertension in infants, birth to less than 1 year of age. However, the Division’s thinking on whether to request studies for calcium channel blockers in infants evolved. Although small sample sizes for hypertensive infants are expected, the Division thinks that studies are feasible to conduct. Furthermore, the Division noted the off-label use of calcium channel blockers in children as young as neonates. To date, the Division does not have sufficient data providing strong evidence that the theoretical risk of cardiovascular collapse from use of calcium channel blockers has been consistently observed in infants exposed to calcium channel blockers. As a result, the Division requested a pediatric study in patients birth to 1 year of age for the treatment of hypertension (please see PMR 3640-2 in the post-marketing section of this review).

A PeRC meeting was held on May 29, 2019. The committee agreed to grant a full waiver for coronary artery disease and to defer studies in pediatric patients ages birth to less than 6 years for hypertension.

5. **Trade name**

On March 26, 2018, the Applicant submitted the proposed proprietary name to IND 116485. This name was denied by the Division of Medication Error Prevention and Analysis.
(DMEPA) on September 21, 2018, due to phonetic similarities with the currently marketed over-the-counter product (b) (4)

On December 3, 2018, the Applicant submitted the proposed proprietary name (b) (4) to the NDA. This name was denied by DMEPA on February 28, 2019, due to orthographic similarities with the currently marketed product (b) (4)

On March 29, 2019, the Applicant submitted the proprietary name KATERZIA to the NDA. This name was considered conditionally acceptable by DMEPA. A Grant Letter was issued on June 20, 2019.

6. Reviews

Below are the conclusions reached by the KATERZIA review team.

a) Divisional Memorandum – July 8, 21019
Recommendation: Approval.
Dr. Stockbridge supported approval of KATERZIA (amlodipine benzoate) oral suspension 1 mg/mL for the treatment of hypertension in adults and children 6 years and older, to lower blood pressure and coronary artery disease [Chronic Stable Angina, Vasospastic Angina (Prinzmetal’s or Variant Angina) and Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40%].
His concurrence can be found in Dr. Hariharan’s CDTL memo.

b) Cross-Discipline Team Leader Memo – July 8, 2019
Recommendation: Approval.
Dr. Hariharan summarized the product quality and clinical pharmacology findings and provided a brief benefit-risk assessment. He concluded that the risk-benefit of KATERZIA when used as directed in the proposed label is not expected to be different compared to NORVASC®.

c) Clinical Pharmacology review – June 4, 2019
Recommendation: Approval.
The Office of Clinical Pharmacology concluded that the results of the BA study (SG05-02) show that both the peak concentration (Cmax) and the area under the curve (AUC) for amlodipine is bioequivalent between KATERZIA and NORVASC®, thus establishing a bridge to borrow the Agency’s previous finding of safety and effectiveness for NORVASC®. There was no effect of food on the pharmacokinetics of amlodipine following administration of KATERZIA with a high fat meal. The lack of food effect for KATERZIA is consistent with the food effect results reported for NORVASC®.

d) Office of Pharmaceutical Quality integrated review – July 3, 2019
Recommendation: Approval
Drug Substance: Amlodipine besylate is a racemic mixture with one chiral center (i.e., 2 enantiomers). The applicant has cross-referenced Type II DMF (b) (4) which was been previously reviewed and found to be adequate.
**Drug Product:** KATERZIA is a ready-to-use aqueous formulation containing 1 mg/mL of amlodipine (equivalent to 1.30 mg of amlodipine benzoate). It is a white to off-white suspension, filled as 150 mL in 185-cc round white, opaque, high-density polyethylene (HDPE) bottles. Pharmaceutical development studies adequately supported the formulation design, including excipient selection and excipient levels.

**Facilities:** The Office of Process and Facilities has recommended an overall approval for all the manufacturing facilities listed in this NDA.

**Microbiology:** KATERZIA is a non-sterile oral suspension and complies with USP <1111>, “Microbiological Examination of Nonsterile Products.” Release testing performed per USP <61> and <62> was adequate. The antimicrobial effectiveness testing (AET) demonstrated acceptable effectiveness.

**Biopharmaceutics:** The Biopharmaceutics review evaluated the in vitro dissolution method and acceptance criterion for KATERZIA, and the need for formulation bridging. The proposed dissolution method and the dissolution acceptance criterion (not less than [90%](#) in 15 minutes) were deemed adequate. In-vitro and/or in-vivo bridging studies were not needed because there was no changes in a) the composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, b) product manufacturing site, and c) manufacturing process in the scale-up. Only one strength (1 mg/mL) was proposed, therefore no biowaver request was necessary.

**Container Closure System:** KATERZIA is packaged as 150 mL in 185-cc high-density polyethylene (HDPE) using components that are routinely used in the pharmaceutical industry for oral dosage forms. No leachables above [0.00](#) µg/mL have been detected when compared to the control. All elements detected by plasma/mass spectrometry testing were below the USP <232> limits. The proposed container closure system was deemed appropriate for the intended use.

**Stability, storage conditions and expiration date:** The Applicant has demonstrated stability for a period of 12 months at 5°C ± 3°C. Supporting data include 24-month long-term stability data. The proposed 24-month shelf-life was supported by development batch data, hence an expiration period of 24 months was granted for KATERZIA when stored refrigerated at 2°C-8°C (36°F-46°F) in the commercial packaging.

7. **Consults**

a) Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (DMEPA) – February 28, 2019, and June 03, 2019

DMEPA reviewed the proposed KATERZIA prescribing information and carton and container labels to identify areas of vulnerability that could lead to medication errors. Several deficiencies that may lead to medication errors were noted. DMEPA provided recommendations to promote the safe use of the product prior to the final labeling discussions with the Applicant.
b) Office of Prescription Drug Promotion (OPDP) – May 23, 2019
OPDP reviewed the proposed prescribing information and carton container labels. There were no comments.

c) Office of Study Integrity and Surveillance (OSIS) – December 4, 2018 and December 18, 2018
The Division of Generic Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance (OSIS) was consulted to inspect the analytical and clinical sites. For the analytical site, OSIS determined that an inspection was not warranted because the site was inspected in August 2018, which fell within the surveillance interval and the final classification for the inspection was No Action Indicated.

Concerning the clinical site, Worldwide Clinical Trials Early Phase Services, LLC, located in San Antonio, Texas, OSIS issued form FDA 483, and the final inspection classification was Voluntary Action Indicated. However, the inspection finding did not impact the reliability of the clinical data.

8. Labeling

Labeling (prescribing information, carton and container labels) was thoroughly reviewed throughout the review cycle. The initial prescribing information recommendations were sent via the Labeling, PMR/PMC Discussion Comments Letter on June 12, 2019.

DMEPA’s and OPQ’s carton and container labels comments were communicated to the Applicant on May 24, 2019 via email. There were no OPDP container label comments to be conveyed.

The Applicant accepted the Agency’s carton and container label comments in an email dated May 29, 2019, followed by an official submission on May 31, 2019.

Additional labeling recommendations were emailed to the Applicant on July 2, 2019, and July 7, 2019. The Applicant accepted all of the Agency’s recommendations in emails dated July 2, 2019 and July 8, 2019.

The final agreed-upon labeling was attached to the approval letter.

9. Post Marketing

The following post marketing requirements were accepted by the Applicant on June 10, 2019, and communicated in the Labeling, PMR/PMC Discussion Comments Letter dated June 12, 2019, as well as the approval letter:

3640-1 Conduct non-clinical toxicity studies in juvenile rats to evaluate developmental toxicity to include assessment of the effects of amlodipine benzoate suspension on reproductive and learning development to support dosing in humans down to birth

<table>
<thead>
<tr>
<th>Final Protocol Submission:</th>
<th>07/2019</th>
</tr>
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<tbody>
<tr>
<td>Study Completion:</td>
<td>07/2020</td>
</tr>
<tr>
<td>Final Report Submission:</td>
<td>01/2021</td>
</tr>
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</table>
Conduct a dose-ranging, safety, tolerability, and efficacy study with amlodipine benzoate oral suspension in hypertensive pediatric patients age birth to less than 6 years of age

Final Protocol Submission: 04 /2021
Study/Trial Completion: 10 /2025
Final Report Submission: 04 /2026

V. CONCLUSION

The review team recommended approval. An approval letter was signed by Dr. Stockbridge on July 8, 2019.
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/

SABRY SOUKEHAL
07/08/2019 05:16:49 PM
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: June 3, 2019
Requesting Office or Division: Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number: NDA 211340
Product Name and Strength: Amlodipine Oral Suspension, 1 mg/mL
Applicant/Sponsor Name: Silvergate Pharmaceuticals, Inc. (Silvergate)
FDA Received Date (via email): May 31, 2019
OSE RCM #: 2018-2140-1
DMEPA Safety Evaluator: Sarah Thomas, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM
The Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised container label and carton labeling for amlodipine oral suspension (Appendix A) to determine if they are 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
We note that Silvergate incorporated all of our recommendations except for the recommendation for the expiration date format on the container label and carton labeling. Silvergate wishes to use the MM/YYYY format for the expiration date “for consistency and their suppliers’ capabilities”. We find their proposed alternative expiration date format acceptable. Silvergate also revised the label and labeling to conform with Patheon’s printer (black box with lot number and expiration date etched out in white). Last, since the proposed product is an oral suspension, Silvergate removed the (b) (4) statement and added “Shake before using” to the label and labeling. We have no further recommendations for the revised container label and carton labeling from a medication error perspective at this time.

a 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.
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/

SARAH E THOMAS
06/03/2019 11:52:12 AM

CHI-MING TU
06/03/2019 12:04:09 PM
Memorandum

Date: May 23, 2019

To: Sabry Soukehal, Regulatory Project Manager
   Division of Cardiovascular and Renal Products (DCRP)

   Michael Monteleone, Associate Director for Labeling, (DCRP)

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

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (amlodipine) Oral Suspension, for oral use

NDA: 211340

In response to DCRP consult request dated October 23, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for TRADENAME (amlodipine) Oral Suspension, for oral use. We note that there is no patient labeling associated with this NDA (although the consult request indicates otherwise).

**PI:** OPDP has reviewed the proposed substantially complete draft PI received by electronic mail from DCRP on May 21, 2019, and we do not have any comments at this time.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 14, 2018, 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.
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/

----------------------------------

ZARNA PATEL
05/23/2019 01:44:50 PM
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***

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>February 28, 2019</th>
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<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Cardiovascular and Renal Products (DCRP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA 211340</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Amlodipine Oral Suspension, 1 mg/mL</td>
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<tr>
<td>Product Type:</td>
<td>Single Ingredient Product</td>
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<tr>
<td>Rx or OTC:</td>
<td>Prescription (Rx)</td>
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<tr>
<td>Applicant/Sponsor Name:</td>
<td>Silvergate Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>FDA Received Date:</td>
<td>September 14, 2018</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2018-2140</td>
</tr>
<tr>
<td>DMEPA Safety Evaluator:</td>
<td>Sarah Thomas, PharmD</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Chi-Ming (Alice) Tu, PharmD, BCPS</td>
</tr>
</tbody>
</table>
1 REASON FOR REVIEW

As a part of the NDA review process, this review evaluates the proposed amlodipine oral suspension container label, carton labeling, 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>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
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<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
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<tr>
<td>Human Factors Study</td>
<td>C-N/A</td>
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<td>ISMP Newsletters</td>
<td>D-N/A</td>
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<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>E-N/A</td>
</tr>
<tr>
<td>Other</td>
<td>F-N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Amlodipine is currently available as 2.5 mg, 5 mg, and 10 mg tablets. Silvergate Pharmaceuticals is proposing an Amlodipine oral suspension, a new dosage form, with a proposed strength of 1 mg/mL. We find the proposed strength in a 150 mL bottle acceptable from a medication error perspective based on the following reasons:

- A 150 mL bottle will provide a 30-day supply based on the labeled dose of 5 mg once daily for pediatric patients 6 years of age and older.
- The proposed concentration of 1 mg/mL is consistent with the 1 mg/mL concentration of 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)]\(^b\).


We note the USP monographs for amlodipine compounded oral suspension and for amlodipine besylate provide the following storage information, respectively: “package in tight, light-resistant containers”; “preserve in tight containers, protected from light”. However, the “protect from light” storage information is not provided on the label and labeling for NDA 211340. We emailed CMC on February 14, 2019 to inquire about the amlodipine oral suspension requiring protection from light and deferred to them on including this storage information in the label and labeling for NDA 211340.

Our review of the container label, carton labeling, and prescribing information (PI) for amlodipine besylate oral suspension 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.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label, carton labeling, and PI for amlodipine oral suspension may be improved to promote the safe use of the product as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

Underlined text in this section indicates our recommendation only.

1. Dosage and Administration Section, Highlights and Full PI
   a. We recommend adding the route to the dosing information provided in the Dosage and Administration Sections of the Highlights and Full PI, as follows:
      i. “Adult recommended starting dose: 5 mg orally once daily...”
      ii. “The usual initial antihypertensive oral dose of TRADENAME Oral Suspension is 5 mg orally once daily,...”

2. Dosage and Administration Section, Full PI
   a. 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:
      i. “Angina: The recommended dose for chronic stable and vasospastic angina is 5 mg to 10 mg once daily,. Most patients will require 10 mg 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 once daily.
In clinical studies, the majority of patients required 10 mg once daily...

3. Dosage Forms and Strengths, Highlights
   a. We recommend revising the description “(b) (4) suspension:” to be consistent with the proposed dosage form “Oral suspension:”.

4. Dosage Forms and Strengths, Full PI
   a. We recommend adding the color (e.g., “white to off-white” per description in Section 16) and taste of the oral suspension to Section 3, Dosage Forms and Strengths to facilitate identification of the oral suspension.

5. How Supplied/Storage and Handling Section
   a. We recommend adding the taste of the oral suspension to Section 16 to facilitate identification of the oral suspension.
   b. We recommend replacing the error-prone symbol (b) (4) c.d with mL in the following statement: “It is supplied as 150 mL in a 185 mL high-density polyethylene (HDPE) bottle...”.

6. Patient Counseling Information, (b) (4) of Full PI, and Patient Information
   a. Add the following statements to (b) (4) and the “How should I take TRADENAME?” section of the Patient Information:

   We recommend this due to evidence that suggests use of an oral syringe may decrease the risk of wrong dose error, particularly when measuring smaller doses.\(^e\)

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4.2 RECOMMENDATIONS FOR SILVERGATE PHARMACEUTICALS, INC.

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

A. General Comments (Container Label & Carton Labeling)
   1. Revise the storage information on the side panels of the container label and carton labeling to “Must store refrigerated at 2°C -8°C (36°F -46°F).” (underline to indicate change and not for implementation)
   2. Replace the proposed proprietary name, [redacted], with a placeholder (e.g., TRADENAME) on the container label and carton labeling because the proposed name, [redacted], was found not acceptable from a safety perspective.
   3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Label
   1. As currently presented, the strength statement on the container label (e.g., 1.0 mg/mL) contains a trailing zero following a decimal point, which is on ISMP’s list of error-prone abbreviations, symbols, and dose designations. Remove the trailing zero (e.g. 1.0 mg) to avoid a ten-fold misinterpretation.
   2. We note the horizontal position of the barcode on the container label. When printed, ensure the barcode is positioned vertically and with enough white space surrounding it so that it is able to be scanned.
   3. We note the storage statement “Avoid exposure to excessive heat and freezing.” on the carton labeling and in the PI Section 16. We recommend adding the statement to the storage information provided on the side panel of the container label if space allows.

---


C. Carton Labeling
   1. Decrease the size of the company logo/graphic on the carton labeling, as it competes in size with the proprietary name.
Table 2 presents relevant product information for Amlodipine oral suspension received on September 14, 2018 from Silvergate Pharmaceuticals, Inc., and the listed drug (LD).

### Table 2. Relevant Product Information for Amlodipine and the Listed Drug

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Amlodipine</th>
<th>Norvasc (Amlodipine Besylate)(^i) (NDA 019787)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval Date</td>
<td>N/A</td>
<td>July 31, 1992</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Amlodipine</td>
<td>Amlodipine besylate</td>
</tr>
</tbody>
</table>
| Indication                            | Calcium channel blocker and may be used alone or in combination with other antihypertensive and antianginal agents for the treatment of:  
  • Hypertension  
    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.  
  • Coronary Artery Disease  
    o Chronic Stable Angina  
    o Vasospastic Angina (Prinzmetal’s or Variant Angina)  
    o Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40% |
| Route of Administration              | Oral       |                                                  |
| Dosage Form                           | Oral Suspension | 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.  
  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.  
  -Pediatric starting dose (6 to 17 years of age): 2.5 mg to 5 mg once daily.  
  -Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrated more rapidly, |

however, if clinically warranted, provided the patient is assessed frequently.

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>150 mL in a 185 mL HDPE bottle with a child-resistant cap and tamper-evident seal.</th>
<th>-2.5 mg tablet: Bottle of 90 -5 mg tablet: Bottles of 90 and 300, unit dose package of 100 -10 mg tablet: Bottle of 90 and unit dose package of 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage</td>
<td>Store refrigerated at 2 °C to 8 °C/36 °C to 46 °C. Avoid freezing and excessive heat.</td>
<td>Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant containers (USP).</td>
</tr>
<tr>
<td>Container Closure</td>
<td>The closure is a 28-mm white child-resistant cap and tamper-evident seal.</td>
<td>Bottle and unit dose package</td>
</tr>
</tbody>
</table>
APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 13, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, “amlodipine” and NDA # “211340”. Our search did not identify any previous reviews.
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, along with postmarket medication error data, we reviewed the following Amlodipine oral suspension label and labeling submitted by Silvergate Pharmaceuticals, Inc.

- Container label received on September 14, 2018
- Carton labeling received on September 14, 2018
- Prescribing Information (Image not shown) received on September 14, 2018

G.2 Label and Labeling Images

Container Label

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

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\[1 \text{ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.}\]
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/s/

SARAH E THOMAS  
02/28/2019 03:01:14 PM

CHI-MING TU  
02/28/2019 03:10:46 PM
MEMORANDUM

DATE: December 18, 2018

TO: Dale Conner, Pharm.D.
Director
Office of Bioequivalence
Office of Generic Drugs

FROM: Xiaohan Cai, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX.

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of studies conducted at Worldwide Clinical Trials Early Phase Services (Worldwide), LLC, San Antonio, TX.
4. Conclusion:

The final inspection classification is Voluntary Action Indicated (VAI).

In addition, the overall performance of the site was adequate and is unlikely to impact the integrity of the data from other studies of similar design.

In addition, studies of similar design conducted between the previous inspection and the end of the current surveillance interval should also be accepted for review by the Agency without an inspection.

Xiaohan Cai, Ph.D.
Senior Staff Fellow

Final Classification:

VAI- Worldwide Clinical Trials Early Phase Services, LLC
San Antonio, TX
FEI#: 3006724658

CC:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Cai

Draft: XHC 12/13/2018
Edit: YMC 12/13/2018; JC 12/16/2018

ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL SITES/Worldwide Clinical Trials Drug Development, San Antonio, TX
Routine inspection of Worldwide Clinical Trials Early Phase Services, LLC, San Antonio, TX.

Non-Responsive

FACTS: 11849415
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/s/

XIAOHAN CAI
12/18/2018

YOUNG M CHOI
12/18/2018

SEONGEUN CHO
12/18/2018