# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211340Orig1s000

# SUMMARY REVIEW

# Cross-Discipline Team Leader Review

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| **Date** | July 5, 2019 |
| **From** | Sudharshan Hariharan |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #** | NDA 211340 |
| **Type** | 505(b)(2) |
| **Applicant** | Silvergate Pharmaceuticals Inc. |
| **Date of Submission** | September 14, 2018 |
| **PDUFA Goal Date** | July 14, 2019 |
| **Proprietary Name / Established (USAN) names** | KATERZIA / Amlodipine besylate |
| **Dosage forms / Strengths** | Oral Suspension / 1 mg/mL |
| **Proposed Indication(s)** | 1. Treatment of hypertension in adults and children 6 years and older<br>2. Treatment of coronary artery disease |
| **Recommendation:** | *'Approval'* |

| **Material Reviewed/Consulted** | |
|---|---|
| Integrated Quality Review (07/03/19) | Monica Cooper, Suong Tran (Drug Substance), Stephanie Emory, Wendy Wilson-Lee (Drug Product), Mark Johnson, Rapti Madurawe (Process and Facility), Kaushalkumar Dave, Jing Li (Biopharmaceutics), Jason God, Denise Miller (Microbiology), Mohan Sapru (Application Technical Lead) |
| Pharmacology-Toxicology Review | NA |
| Clinical Pharmacology Review (06/04/19) | Anusha Ande, Sudharshan Hariharan |
| Clinical Review | NA |
| Division of Medication Error Prevention and Analysis Reviews (02/28/19, 06/03/19, 06/20/19) | Sarah Thomas, Chi-Ming Tu, Danielle Harris |
| Office of Study Integrity and Surveillance (12/04/18, 12/18/18) | Angel Johnson, Xiaohan Cai, Young Choi, Seongeun Cho |
| Office of Prescription Drug Promotion Review (05/23/19) | Zarna Patel |

## 1. Introduction

On September 14, 2018, Silvergate Pharmaceuticals Inc. submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for KATERZIA (the

final agreed upon tradename), an oral suspension of amlodipine, for the following proposed indications:

- For treatment of hypertension in adults and in children six years and older, to reduce blood pressure

- Treatment of coronary artery disease (CAD): chronic stable angina, vasospastic angina (Prinzmetal's or variant angina), and angiographically-documented CAD in patients without heart failure or an ejection fraction of < 40%.

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, NORVASC® tablets (NDA 19787, approved 1992). No new clinical efficacy data are submitted in this application and no new claims are being sought with this application.

## 2. Background

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is a peripheral-arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral-vascular resistance and reduction in blood pressure. In adults the recommended starting dose is 5 mg/day with a maximum dose of 10 mg/day. Amlodipine (2.5 to 5 mg daily) is effective in lowering blood pressure in pediatric patients 6 to 17 years. The effect of amlodipine on blood pressure in patients less than 6 years of age is not known. The recommended dose range for patients with CAD is 5 to 10 mg once daily. In clinical studies, the majority of patients required 10 mg.

The applicant has developed a ready-to-use Amlodipine Oral Suspension to replace the requirement of extemporaneous compounding of tablets into a suspension by either pharmacists or caregivers for treatment in patients who have difficulty swallowing tablets. The applicant proposes the same dose and dosing regimen for the oral suspension of amlodipine as approved for NORVASC for the proposed indications.

## 3. Product Quality

Office of Product Quality (OPQ) recommends approval of the application from a quality perspective. The applicant has satisfactorily addressed all the deficiencies that were communicated during the review. There are no unresolved issues at this time.

*Drug substance*:
The applicant has cross-referenced Type II DMF (b) (4) which has been reviewed and found to be adequate. There is one chiral center; therefore, the drug substance exists as a racemic mixture (b) (4) (b) (4) Based on the manufacturing process, there is potential to form (b) (4) impurities. However, when tested for these impurities using a validated analytical assay, (b) (4) were found to be no more than (NMT) (b) (4) ppm, well below the calculated PGI limit of NMT (b) (4) ppm. Based on stability data, the drug substance has a retest period of

(b) (4) months when stored (b) (4) Further, the OPQ review states that based on drug substance specification and batch analysis data, the control strategy is adequate to assure quality of the synthesized drug substance.

*Drug product*:
The proposed drug product is a ready-to-use aqueous formulation containing 1 mg/mL amlodipine (1.3 (b) (4) mg/mL amlodipine besylate). It is a white to off-white suspension, filled as 150 mL in 185-cc round white, opaque, high-density polyethylene bottles. (b) (4) Because of this, the OPQ review recommends revising the carton and container labels to reflect the primary salt form i.e., amlodipine benzoate, in the final manufactured product. In conclusion, the OPQ review states that the pharmaceutical development studies adequately support the formulation design, including excipient selection and excipient levels.

(b) (4)

The OPQ review also concludes that the container closure system is appropriate for the intended use.

(b) (4)

*Expiration Date and Storage Conditions*:
Based on the OPQ's assessment of stability data, the proposed product shelf-life of 24 months, when stored refrigerated at 2 to 8°C (36 to 46°F) in the commercial container closure system, is acceptable.

*Facilities review/inspection*:

All currently listed manufacturing facilities are deemed acceptable by Office of Process and Facilities.

## 4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted as part of the application. All nonclinical findings with NORVASC can be borrowed based on an acceptable bridge to the listed drug.

## 5. Clinical Pharmacology

Office of Clinical Pharmacology (OCP) recommends approval of the oral suspension of amlodipine with or without food. The applicant conducted a randomized, three-way crossover study (Study No. SG05-02) characterizing the pharmacokinetics of amlodipine following administration of the oral suspension and the listed drug, NORVASC, under fasted conditions. The study also assessed the effect of food for the oral suspension. The results show that both the peak concentration ($C_{max}$) and the area under the curve (AUC) for amlodipine is bioequivalent between the oral suspension and NORVASC, thus establishing a bridge to borrow Agency's previous finding of safety and effectiveness for NORVASC. There was no effect of food on the pharmacokinetics of amlodipine following administration of the oral suspension with a high fat meal. The lack of food effect for the oral suspension is consistent with the food effect results reported earlier for NORVASC.

*Site Inspection*:
OCP requested inspection of the clinical (San Antonio, TX) and bioanalytical site (b) (4) for the relative BA study SG05-02. OSIS recommends accepting data from these studies.

## 6. Clinical/Statistical- Efficacy

As discussed under Clinical Pharmacology, the relative bioavailability study provides the bridge to the efficacy findings of the listed drug, NORVASC.

## 7. Safety

This application primarily relies on the Agency's previous determination of safety for the listed drug, NORVASC.

## 8. Advisory Committee Meeting

The application does not raise significant issues regarding the safety or effectiveness of the drug; hence, no Advisory Committee Meeting was held or needed.

## 9. Pediatrics

This application triggers Pediatric Research Equity Act (PREA) because it is a new dosage form. The applicant is seeking the following waivers of pediatric studies:

- *Coronary artery disease (0 to 16 years)*: On the basis that studies are impossible or highly impracticable as this disease occurs rarely in children. The pediatric review committee (PeRC) agreed.

Given that NORVASC is approved for the treatment of hypertension in pediatric patients 6 to <17 years of age, studies are not needed to establish safety and effectiveness in this population.

The applicant originally requested a deferral of pediatric studies in patients (b) (4) with hypertension, and a waiver for patients (b) (4) in the agreed initial pediatric study plan (iPSP). However, after internal discussions with Division of Pediatric and Maternal Health (DPMH), the Division's (Division of Cardiovascular and Renal Products, DCRP) thinking on whether to request studies for calcium channel blockers in infants evolved. The following is captured as DCRP's position in the PREA assessment form (DARRTS date: 05/17/19):

"Although we expect small sample sizes for hypertensive infants, we think that studies are still feasible to conduct. Furthermore, there is already off-label use of calcium channel blockers in children as young as neonates. To date, we do 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."

Therefore, the need for conducting studies in pediatric hypertension patients down to birth was discussed with the applicant. The applicant agreed and revised the iPSP to request deferral of pediatric studies in patients from birth to 6 years of age with hypertension. The PeRC agreed to the modified deferral.

The Division recommends the following studies as post-marketing requirements (PMR):

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

- Conduct a dose ranging, safety, tolerability, and efficacy study with Amlodipine Oral Suspension in hypertensive pediatric patients age birth to less than 6 years of age.

Because calcium ions and L-type voltage dependent calcium channels are involved in multiple physiological processes from embryonic development through adulthood, including those in neurosecretion and hypothalamic rhythm generation, the Division requests a juvenile toxicity study applicable to humans (b) (4) to assess for effects on reproductive development prior to conducting a clinical study in patients <6 years of age.

## 10. Other Relevant Regulatory Issues

None.

# 11. Labeling

There are no unresolved labeling issues. An agreement with the applicant has been reached on the proposed alterations to the label.

*Proprietary name*: The latest proposed proprietary name, KATERZIA, is accepted by DMEPA. The other two proprietary names previously proposed by the applicant, (b) (4), were denied by DMEPA because they looked or sounded similar to other currently marketed products.

# 12. Recommendations/Risk Benefit Assessment

*Recommended Regulatory Action*
Approval

*Risk Benefit Assessment*
For the indications sought, the risk-benefit of KATERZIA when used as directed in the proposed label is not expected to be different compared to NORVASC.

*Recommendation for Postmarketing Risk Evaluation and Management Strategies*
None

*Recommendation for other Postmarketing Requirements (PMR) and Commitments*

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

- Conduct a dose ranging, safety, tolerability, and efficacy study with Amlodipine Oral Suspension in hypertensive pediatric patients age birth to less than 6 years of age.

*Recommended Comments to Applicant*
As noted under the 'Product Quality' section of this memo, OPQ's feedback on the Comparability Protocol should be sent in an advice letter to the applicant.

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**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.**

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/s/

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