CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211340Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 211340: Katerzia (amlodipine) Oral Suspension

OPQ Integrated Quality Review

Recommendation: Recommended for Approval

Drug Name/Dosage Form	Katerzia (amlodipine) Oral Suspension
Strength	1.0 mg/mL of amlodipine
Route of Administration	Oral solution
Indication	The proposed product is indicated for the treatment of hypertension in adults and children (6 years of age and older), and for the treatment of coronary artery disease in adult patients
Rx/OTC Dispensed	Rx
Applicant	Silvergate Pharmaceuticals, Inc.
Submissions (s) Reviewed	NDA 211340, DMF (b) (4), and all submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	ONDP/DNDPI/NDPBI
Drug Product, Labeling, Environmental Assessment	Stephanie Emory	ONDP/DNDPI/NDPBI
Process and Facility	Mark Johnson	OPQ/OPF/DPAI/PABI
Biopharmaceutics	Kaushalkumar Dave	ONDP/DB/BBI
Microbiology	Jason God	OPQ/OPF/DMA/MABII
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Laboratory (OTR)	N/A	
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

RELATED/SUPPORTING DOCUMENTS:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
DMF	Type II DMF #: (b) (4)	Previously reviewed and found adequate

CONSULTS:
None.

(Continued on next pages)

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 211340 i.e., Katerzia (Amlodipine Oral Suspension) is recommended for approval. As part of this action, an expiration period of 24 months is granted for the proposed product when stored refrigerated at 2°C-8°C (36°F-46°F) in the commercial packaging.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Background, and Quality Assessment Summary

The applicant, Silvergate Pharmaceuticals, Inc., has sought U.S. marketing approval for Katerzia (amlodipine) Oral Suspension under the provisions of Section 505(b)(2) of the Federal Food and Cosmetic Act. To support the approval of the proposed product, the applicant is relying on Agency's previous finding of safety and effectiveness for the Listed Drug (LD), Norvasc® (amlodipine) tablets (NDA 019787, approved July 31, 1992). The proposed ready-to-use formulation is indicated for the treatment of hypertension in adults and children (6 years of age and older), and for the treatment of coronary artery disease in adult patients. The LD Norvasc® is FDA-approved for the above-mentioned indications. The amlodipine oral suspension is a 'convenience dosage form' developed for patients who have difficulty swallowing tablets. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, potency, and stability.

A. Drug Substance (Amlodipine Besylate) Quality Summary

For CMC details concerning the drug substance, the applicant has cross-referenced Type II DMF (b) (4), which was been previously reviewed and found to be adequate (see DMF Review #16, dated 02-May-2019, D. Skanchy). Based on the information provided in the NDA, the drug substance, which has one chiral center (i.e., 2 enantiomers), is a racemic mixture. The well-controlled drug substance manufacturing process (b) (4) (b) (4) The applicant has indicated (b) (4)

(b) (4) based on DMF holder's manufacturing process. The DMF holder's drug substance specification as well as the revised specification by drug product manufacturer (b) (4) for the incoming drug substance both comply with the current USP monograph for amlodipine besylate. Validation of non-compendial analytical procedures is adequate. A (b) (4) month retest period for the drug substance, (b) (4) s appropriate based on stability data. Based on the information provided in the NDA and CMC details cross-referenced to DMF (b) (4) the control strategy is adequate to assure the quality of the incoming drug substance and its suitability for the manufacture of the drug product.

B. Drug Product (Amlodipine Oral Suspension) Quality Summary

B.1. Product Design, and Release Specification: Amlodipine Oral Suspension is a ready-to-use aqueous formulation containing 1.0 mg/mL of amlodipine (1.3 (b) (4) mg/mL as amlodipine besylate). It is a white to off-white suspension, filled as 150 mL in 185-cc round white, opaque, high-density polyethylene (HDP) bottles. Pharmaceutical development studies adequately support the formulation design, including excipient selection and excipient levels. No novel or human/animal-origin excipients are used in the formulation. All excipients are compendial except (b) (4) Simethicone (b) (4) (b) (4) The maximum daily dose (MDD) of this excipient is (b) (4) mg (based on amlodipine MDD (b) (4) mL), which is below the IID levels for simethicone USP (b) (4) and (b) (4) NF (b) (4) All other excipients in the proposed formulation are below IID levels for previous oral products, by both concentration and quantity per dosage unit. Risk assessments for (b) (4) and elemental impurities conclude that no additional controls are necessary.

(b) (4)

Specification: The product release specification, involving testing of all the product critical quality attributes (CQAs), is adequate to ensure the consistent product quality. The non-compendial analytical procedures used for testing the drug product such as reverse-phase HPLC and UPLC have been validated according to ICH guidelines. Specifically, the acceptance limits for impurities are appropriately narrower at release, while the relatively wider acceptance limits for impurities per stability specification are in compliance with the USP monograph for amlodipine besylate tablets. (b) (4) Based on this assessment, the elemental impurities in the proposed product do not exceed the ICH Q3D-compliant permitted daily exposure (PDE) limits. Hence, no release testing for elemental impurities is required. The applicant has committed to update the elemental impurities assessment if changes in process, ingredients or product manufacturing site is made.

In conclusion, the product design, selection of excipients and control of product quality via release testing are adequate.

B.2. Manufacturing: Briefly, the product manufacturing involves (b) (4) All unit operations have been found to have a low level of risk on (b) (4) and final drug product quality attributes. The in-process control tests conducted at each critical step per the proposed acceptance criteria, and the master batch records are adequate. The overall control strategy is therefore adequate to ensure consistent production of finished product capable of meeting pre-determined acceptance criteria.

B.3. Microbiological Aspects: The drug product is a non-sterile oral suspension and complies with USP <1111>, "Microbiological Examination of Nonsterile Products." The microbiological testing is included in release and stability specifications. Release testing performed per USP <61> and <62> is adequate for the proposed product. (b) (4) The antimicrobial effectiveness testing (AET) on product formulated at the lowest label claim for (b) (4) demonstrates acceptable (b) (4) Further, stability data provided for 3 registration

batches show acceptable AET results through 12 months of testing. The applicant has committed to performing AET at the end of shelf-life for all 3 registration batches.

B.4. Biopharmaceutics Aspects: The applicant has indicated that amlodipine is a BCS Class 1 compound; however, no permeability data have been provided. However, no BCS designation request has been submitted by the applicant and no designation for amlodipine has been determined by the Agency. To establish bioequivalence, the applicant has studied relative bioavailability of the proposed product under fasted and fed conditions versus the LD under fasted conditions in healthy adults. The results of the study will be evaluated by the Office of Clinical Pharmacology. The Biopharmaceutics review evaluated the: i) *in vitro* dissolution method and acceptance criterion for the proposed drug product, and ii) need for formulation bridging.

Dissolution Acceptance Criteria: Because the originally proposed dissolution acceptance criterion of 'Not less than (NLT) (b) (4)% (Q) at (b) (4) minutes' was permissive and not supported by the data, the applicant was recommended to revise the dissolution acceptance criterion to 'NLT(b) (4)% (Q) at 15 minutes'. To comply, the applicant has revised the dissolution acceptance criterion accordingly. The applicant's selection of the dissolution medium (b) (4) is justified because the proposed product is an immediate-release suspension intended to release the drug in the stomach where the pH condition is similar to (b) (4) (the proposed dissolution medium). Based on the provided information/data, the proposed dissolution method and the revised dissolution acceptance criterion (not less than (b) (4)% (Q) in 15 minutes) is adequate for quality control testing of the proposed product.

Formulation Bridging: *In-vitro and/or in-vivo* bridging studies are not needed for the proposed product as there is no changes in: a) 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) is proposed under the current NDA and therefore no biowaiver request is submitted or necessary.

In conclusion, the Biopharmaceutics information provided to support this NDA submission is adequate.

B.5. Container Closure System: Amlodipine Oral Suspension is packaged as 150 mL in 185-cc high-density polyethylene (HDPE) bottles with 28-mm, (b) (4) child-resistant, (b) (4) caps with a (b) (4) (b) (4) induction seal. These components are routinely used in the pharmaceutical industry for oral dosage forms. The HDPE (b) (4) for the bottles and (b) (4) for the caps comply with the requirements of 21 CFR Part 177. The container closure system complies with USP <661> for performance of plastics and USP <671> container permeation requirements for multiple-unit containers. Regarding extractables, no nonvolatile, semi-volatile, or volatile compounds have been detected (b) (4) when evaluating the HDPE bottles, labels, or ink migration. No leachables above (b) (4) µg/mL have been detected when compared to the control. Analysis

of [redacted] has detected [redacted] above [redacted] ppb in [redacted] HDPE bottles. [redacted] above [redacted] ppb have been detected in the suspension stored in labeled HDPE bottles. All elements are below the USP <232> limits. The proposed container closure system is appropriate for the intended use.

B.6. Stability, Storage Conditions and Expiration Date: Based on stability studies, the applicant has demonstrated stability for the proposed product for a period of 12 months at $5^0C \pm 3^0C$. Supporting data include 24-month long-term stability data for 3 development batches and statistical analysis for each product attribute. [redacted] in accordance with ICH guidance Q1A, the 3 registration batches are representative of the commercial product in terms of formulation, batch size, and packaging, and each has been manufactured using a different drug substance batch. The proposed 24-month shelf-life is within the allowances in ICH Q1E and is supported by development batch data and the statistical analysis provided, which includes evaluation of amlodipine assay, sodium benzoate assay, impurities, pH, and dissolution results for registration, pilot, and full-scale development batches. Hence, an expiration period of 24 months is granted for the proposed product when stored refrigerated at 2°C-8°C (36°F-46°F) in the commercial packaging. Given the well-known photosensitivity of amlodipine, no product photostability study has been conducted.

C. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended an overall approval for all the currently listed manufacturing facilities concerning this NDA.

[redacted]

E. Environmental Assessment: The applicant's claim of categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

F. Any Special Product Quality Labeling Recommendations:

The following recommendations have been communicated to the applicant:

1. Because the final product is predominantly a suspension of amlodipine benzoate, revise the equivalency statement on the carton and container labels as follows: "Each 1 mL contains 1.XX mg of amlodipine benzoate, equivalent to 1 mg amlodipine."
2. Revise the description of the identifying characteristics of the dosage forms (Section 3) by stating: "white to off-white suspension".
3. Under Section 16 How Supplied/Storage and Handling, include the statement: "protect from light".

F. Life Cycle Knowledge Information

See Final Risk Assessment on the next page.

Final Risk Assessment:
NDA 211340 (Amlodipine Oral Suspension)

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment/site	Low (L)	(b) (4)	Acceptable	(b) (4)
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Low (L)		Acceptable	N/A

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Physical Stability (phase separation)	• Formulation • Raw materials • Process parameters • Scale/ equipment/ site	Low (L)	(b) (4)	Acceptable	Any proposed changes to formulation, manufacturing or the control strategies will need to be evaluated for possible impact on product CQAs
Dosing Accuracy	• Formulation • Dosing device • Process parameters • Scale/equipment/site	Low (L)	(b) (4)	Acceptable	N/A
Palatability	• Formulation • Excipient change • Process parameters Scale/equipment/site	Moderate (M)	(b) (4)	Acceptable	N/A
Leachables	• Formulation • Container closure • Process parameters Scale/equipment/site	Moderate (M)	(b) (4)	Acceptable	N/A

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equipment/site	Low (L)	(b) (4)	Acceptable	N/A

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From Chemistry, Manufacturing and Controls (CMC)/quality perspective, NDA 211340 (Amlodipine Oral Suspension) is recommended for approval. An expiration period of 24 months is granted for the proposed product when stored refrigerated at 2°C-8°C (36°F-46°F) in the commercial packaging.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products
ONDP/DNDPI/NDPBI

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LABELING

I. Package Insert ("Draft Labeling Text – MS Word" submitted 14Sep2018)

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title	
Proprietary name and established name	TRADENAME (amlodipine) Oral Suspension, for oral use.
Dosage form, route of administration	
Dosage Forms and Strengths	
Summary of the dosage form and strength	Liquid suspension: 1 mg/mL

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	None

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
Available dosage forms	TRADENAME Oral Suspension contains 1 mg/mL of amlodipine (equivalent to 1.3 (b) (4) mg of amlodipine besylate) in an aqueous, liquid suspension. *Revise to include "white to off-white suspension"*
Strengths: in metric system	
Active moiety expression of strength with equivalence statement (if applicable)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	

4. Section 11 Description

Item	Information Provided in NDA
Proprietary name and established name Dosage form and route of administration Active moiety expression of strength with equivalence statement (if applicable)	TRADENAME Oral Suspension, containing 1 mg/mL of amlodipine, is a ready-to-use formulation of amlodipine besylate (1.3(b) mg/mL) *Revise for consistency with bottle and carton labels: "TRADENAME Oral Suspension is a ready-to-use formulation containing 1 mg of amlodipine (equivalent to 1.3(b) mg amlodipine besylate) per mL."*
Inactive ingredients listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Inactive ingredients include (b) (4) water, citric acid, sodium citrate, sodium benzoate, sucralose, silicon dioxide colloidal, simethicone (b) (4), polysorbate 80, hypromellose (b) (4) and sodium hydroxide (b) (4) *Use USP names except fo* (b) (4) (b) (4)
Pharmacological/ therapeutic class	long-acting calcium channel blocker
Chemical name, structural formula, molecular weight	Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, (b) (4) Its empirical formula is $C_{20}H_{25}CIN_2O_5$ (b) (4), and its structural formula is [see submission for image].
Other important chemical or physical properties (such as pKa or pH)	Amlodipine besylate is a white crystalline powder with a molecular weight of (b) (4). It is a white to off-white suspension. *Revise for consistency with bottle and carton labels: "TRADENAME Oral Suspension is a ready-to-use formulation containing 1 mg of amlodipine (equivalent to 1.3(b) mg amlodipine besylate) per mL."*

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
Strength of dosage form Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	TRADENAME (amlodipine) Oral Suspension is a white to off-white, aqueous suspension that contains 1 mg of amlodipine per milliliter (equivalent to 1.3(b) mg of amlodipine besylate). It is supplied as 150 mL in a 185-cc high-density polyethylene (HPDE) bottle with a child-resistant cap and tamper-evident seal. **SHAKE BEFORE USING**. NDC 52652-5001-1
Special handling (e.g., protect from light)	Avoid freezing and excessive heat. *Include a statement to protect from light.*
Storage conditions	TRADENAME (amlodipine) Oral Suspension, 1 mg/mL, should be stored at refrigerated (2°C to 8°C/36°F to 46°F).
Manufacturer/ distributor name (21 CFR 201.1(h)(5))	Manufactured for: Silvergate Pharmaceuticals, Inc. 6251 Greenwood Plaza Blvd., (b) (4) Greenwood Village, CO 80111

(b) (4)

Reviewer's Assessment of Package Inserts: ***Adequate, pending the applicant's acceptance of the revisions noted above in red.***

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2. Carton Label

Item	Information provided in Pouch and Carton Labels
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	See representative examples above *Add a statement to protect from light.*
Dosage strength	
Net contents	
"Rx only" displayed prominently on the main panel	
NDC number (21 CFR 207.35(b)(3)(i))	
Lot number and expiration date (21 CFR 201.17)	
Storage conditions	
Bar code (21CFR 201.25)	
Name of manufacturer/distributor	

Reviewer's Assessment of Labels: ***Adequate, pending the applicant's acceptance of the revisions noted above in red.***

Stephanie Emory

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Comments: clean version, no changes

Wendy Wilson- Lee

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BIOPHARMACEUTICS

PRODUCT BACKGROUND

NDA: 211340; 505(b)(2)
Drug Product Name / Strength: Amlodipine Oral Suspension / 1 mg/mL
Route of Administration: Oral
Indication: Treatment of hypertension
Submission Date: 09/14/2018 (Original)
Applicant Name: Silvergate Pharmaceuticals, Inc.

BACKGROUND

The proposed product, a ready-to-use Amlodipine Oral Suspension, 1 mg/mL, is a 'convenience dosage form' developed for patients who have difficulty swallowing tablets. It has 1.0 mg/mL of amlodipine (equivalent to 1.3(b) mg of amlodipine besylate) and is indicated for 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%. The listed drug (LD) is Norvasc® (Amlodipine) 5 mg Tablets under NDA 019787 approved for the same indications as the proposed product.

The submission of this 505(b)(2) NDA is supported by a randomized, single-dose, three-way crossover, pivotal bioavailability study (# SG05-02). The objective of this study was to assess the relative bioavailability of a test formulation of a single 5 mg dose of Amlodipine Oral Suspension, 1 mg/mL, (b) (4) for Silvergate) under fasted and fed conditions versus Norvasc® (Amlodipine) 5 mg Tablets, under fasted conditions in healthy adults. The current Biopharmaceutics review is focused on evaluation of (1) the proposed dissolution method and acceptance criterion, and (2) formulation bridging, as presented below.

REVIEW SUMMARY

Dissolution Method: The proposed product is an immediate-release, ready-to-use suspension. Amlodipine has very high solubility in the physiological pH range. The proposed dissolution method [500 mL of 0.01N HCl using USP Apparatus 2 (paddle) at 25 rpm] is similar to the one described in the USP Monograph for Amlodipine Tablets, (b) (4) (b) (4) (b) (4) (b) (4) . (b) (4) (b) (4)

(b) (4)

(b) (4) Therefore, the proposed dissolution method is acceptable for quality control testing of the proposed product.

Dissolution Acceptance Criteria: The Applicant's originally proposed dissolution acceptance criterion of 'Not less than (NLT) (b) (4)% (Q) at (b) (4) minutes' was permissive and not supported by the data. Based on the provided information/data, the Applicant was recommended to revise the dissolution acceptance criterion to 'NLT(b) (4)% (Q) at 15 minutes'. The Applicant accepted the FDA recommendation and revised the dissolution acceptance criterion accordingly. The Applicant's new dissolution acceptance criterion (not less than (b) (4)% (Q) in 15 minutes) is adequate for quality control testing of the proposed product.

Formulation Bridging: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

Conclusion and Recommendation: From a Biopharmaceutics perspective, Amlodipine Oral Suspension, 1 mg/mL, is adequate and recommended for **APPROVAL**.

The approved dissolution method and acceptance criterion for the quality control of the finished immediate release drug product at batch release and during stability testing are summarized in Table 1.

Table 1: FDA's Approved Dissolution Method and Acceptance Criterion for Amlodipine Oral Suspension / 1 mg/mL

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	25 rpm
Volume	500 mL
Medium	0.01N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT (b) (4)% (Q) in 15 minutes

Primary Biopharmaceutics Reviewer Name

Kaushalkumar Dave, Ph.D.
Division of Biopharmaceutics, ONDP, OPQ

I concur with Dr. Dave's Biopharmaceutics assessment and recommendation.

Secondary Reviewer Name
Jing Li, Ph.D.
Division of Biopharmaceutics, ONDP, OPQ

BIOPHARMACEUTICS ASSSESSMENT

1. LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	09/14/2018	Original NDA Submission
0003	01/11/2019	Quality/Response to Information Request
0003	03/25/2019	Quality/Response to Information Request

2. DRUG PRODUCT

The proposed product is an immediate-release, ready-to-use aqueous suspension with 1.0 mg/mL of amlodipine (equivalent to 1.3(b) mg of amlodipine besylate). The Applicant found that (b) (4) (b) (4) (b) (4) The composition of the proposed product is provided in ***Appendix 1***.

To establish bioequivalence, the Applicant studied relative bioavailability of the proposed/test product (a single 5 mg dose of Amlodipine Oral Suspension, 1 mg/mL) under fasted and fed conditions versus Norvasc (amlodipine) 5 mg tablets (LD) under fasted conditions in healthy adults. The results of the study (SG05-02) are summarized in Appendix 2 and will be evaluated by the Office of Clinical Pharmacology.

3. BCS DESIGNATION: *NOT APPLICABLE*

Solubility

The Applicant studied the solubility of amlodipine besylate and amlodipine benzoate in the physiological pH range. The results of the experimental solubility study, summarized in Table 2, indicate that both, amlodipine besylate and amlodipine benzoate, are highly soluble per the BCS criteria.

Table 2: Aqueous Solubility of Amlodipine Salts

Amlodipine Besylate (mg/mL)				
	pH 1.2	pH ~2	pH 4.5	pH 6.8
Sample 1	2.9	2.3	2.4	1.1
Sample 2	3.0	2.3	2.4	1.1
Average	2.9	2.3	2.4	1.1
Amlodipine Benzoate (mg/mL)				
	pH 1.2	pH ~2*	pH 4.5	pH 6.8
Sample 1	4.0	4.4	2.0	1.1
Sample 2	3.6	4.4	2.0	1.1
Average	3.8	4.4	2.0	1.1
*there was no solid visible in the vial after equilibration indicating the solubility value is likely to be greater than 4.4				

Permeability

The Applicant stated that amlodipine is a BCS Class 1 compound; however, the Applicant did not provide any permeability data. It is important to note that no BCS designation request has been submitted by the Applicant and no designation has been determined by the FDA for amlodipine.

4. DISSOLUTION INFORMATION

Selection of the dissolution method

(b) (4)

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(b) (4)

(b) (4)

Based on the above studies the Applicant proposed the same dissolution method as described in the USP Monograph for Amlodipine Tablets [500 mL of 0.01N HCl using USP Apparatus 2 (paddle) at (b) (4) rpm] for quality control testing of the proposed product.

Reviewer's Assessment

The drug substance solubility data (Table 2) indicate that amlodipine benzoate and amlodipine besylate ate highly soluble in the physiological pH range. The Applicant's selection of the dissolution medium (0.01N HCl) is justified because the proposed product is an immediate-release suspension intended to release the drug in the stomach where the pH condition is similar to 0.01N HCl (the proposed dissolution medium). Also, the Applicant's selection of USP Apparatus 2 is justified as it is a suitable and hence the most commonly used USP apparatus for dissolution testing of suspensions.

(b) (4)

(b) (4) The Applicant reported that the dissolution of the proposed product was

(b) (4)

(b) (4)

(b) (4) Based on the provided information/data, the Applicant's proposed dissolution method (Table 1) is adequate for quality control testing of the proposed product.

Selection of the Dissolution Acceptance Criterion

In the original submission, the Applicant proposed the dissolution acceptance criterion of 'NLT (b) (4)% (Q) at (b) (4) minutes' for quality control testing of the proposed product. However, based on the (b) (4) dissolution of the proposed product, the Applicant was recommended (via an IR sent on 03/11/2019) to implement the dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 15 minutes'. In response (dated 03/25/2019[2]), the Applicant accepted the FDA recommendation and implemented the dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 15 minutes' for quality control testing of the proposed product. The Applicant's response is adequate.

5. FORMULATION BRIDGING

In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

[2] Application 211340 - Sequence 0007 - Quality Information Amendment (SN0007; 2019Mar25; Qualify Information Amendment - Response to Request)
[3] Application 211340 - Sequence 0010 - Quality Information Amendment (SN0010; 2019May15; Quality Information Amendment - Response to Request)

6. BIOWAIVER REQUEST

Only one strength (1 mg/mL) is proposed under the current NDA and therefore no biowaiver request is submitted or is necessary.

7. LIST OF DEFICIENCIES

None

Appendix 1

Table: Composition of Amlodipine Oral Suspension, 1 mg/mL

Component	Grade	Function	mg/mL
Amlodipine besylate	USP	Active ingredient	1.3 (b) (4)
Simethicone (b) (4)	USP[b]	(b) (4)	(b) (4)
Sodium benzoate	NF		
Citric acid, (b) (4)	USP		
Sodium citrate, (b) (4)	USP		
Sucralose	NF		
Silicon dioxide colloidal (b) (4)	NF		
Polysorbate 80	NF		
Hypromellose (b) (4)	USP		
Citric acid (b) (4)	USP		(b) (4)
Sodium hydroxide (b) (4)	NF		
(b) (4) water	USP		
NF = National Formulary; *qs* = quantity sufficient; USP = United States Pharmacopeia.			
(b) (4)			
Please refer to DMF (b) (4) A letter of authorization is included in *section 1.4.2.*			
(b) (4)			

Appendix 2

Summary of Pivotal Bioavailability Study# SG05-02

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route)	Subjects (M/F) Age: mean (Range)	Mean Parameters (SD) Single 5 mg Doses					
					C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h·ng/mL)	AUC_{∞} (h·ng/mL)	$t_{1/2}$ (h)	C_{last} (ng/mL)
SG05-02	To assess the relative bioavailability of a test formulation of a single 5-mg dose of amlodipine oral suspension, 1 mg/mL, under fasted and fed conditions versus Norvasc (amlodipine) 5-mg tablets under fasted conditions in healthy adults	Single-dose, open-label, randomized, 3-period, 3-treatment, crossover	A: Amlodipine Oral Solution, 5 mg (fasted) (n = 22) B: Norvasc Tablet, 5 mg (fasted) (n = 22) C: Amlodipine Oral Solution, 5 mg (fed) (n = 21)	Total subjects: 24 M/F: 14/10 Mean age: 37.4 years (range 23 to 55)	Treatment A: Amlodipine Oral Solution (Fasted)					
					2.71 (0.803)	7.78 (1.87)	139.1 (51.62)	162.0 (59.15)	45.98 (13.51)	0.337 (0.088)
					Treatment B: Norvasc Tablet (Fasted)					
					2.75 (0.916)	7.69 (1.83)	139.4 (58.85)	163.4 (66.91)	48.46 (14.75)	0.337 (0.093)
					Treatment C: Amlodipine Oral Solution (Fed)					
					2.43 (0.668)	10.15 (2.87)	136.9 (49.93)	160.3 (61.15)	46.86 (14.18)	0.332 (0.085)

AUC_{∞} = area under the concentration-time curve from time-zero extrapolated to infinity; AUC_{last} = area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; C_{last} = last quantifiable concentration; C_{max} = maximum concentration in plasma; SD = standard deviation; T_{max} = time to maximum concentration; $t_{1/2}$ = terminal elimination half-life.

a

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MICROBIOLOGY

Product Background: The drug product is a non-sterile oral suspension indicated for the treatment of hypertension.

NDA: 211340

Drug Product Name / Strength: Amlodipine oral suspension / 1 mg/mL

Route of Administration: Oral

Applicant Name: Silvergate Pharmaceuticals, Inc.

Manufacturing Site:
(b) (4)

Method of Sterilization: Non-sterile

Review Recommendation: Adequate

Review Summary: Drug product is a non-sterile oral suspension developed as an alternative for individuals who have difficulty swallowing tablets. This review covers antimicrobial effectiveness testing and microbial limits.

List Submissions Being Reviewed:
09/14/2018
01/18/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The subject drug product was developed as an alternative to the existing RLD, Norvasc (tablet), to eliminate the need for the compounding of tablets into suspension form for those individuals with difficulty swallowing tablets.

Concise Description Outstanding Issues Remaining: (None)

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): 1

S Drug Substance

N/A. Drug substance is supplied non-sterile.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Drug product is a white suspension, filled as 150 mL in 185 cc HDPE bottles.

- **Drug product composition –**

Table 1: Composition of Amlodipine oral suspension

Table 3.2.P.1-1. Composition of Amlodipine Oral Suspension			
Component	**Grade**	**Function**	**mg/mL**
Amlodipine besylate	USP	Active ingredient	1.3 (b) (4)
Simethicone (b) (4)	USP[b]	(b) (4) (b) (4)	
Sodium benzoate	NF		
Citric acid, (b) (4)	USP		
Sodium citrate, (b) (4)	USP		
Sucralose	NF		
Silicon dioxide colloidal (b) (4)	NF		
Polysorbate 80	NF		
Hypromellose (b) (4)	USP		
Citric acid, (b) (4)	USP	(b) (4)	
Sodium hydroxide (b) (4)	NF		
(b) (4) water	USP		
NF = National Formulary; *qs* = quantity sufficient; USP = United States Pharmacopeia			
(b) (4)			
Please refer to DMF (b) (4) A letter of authorization is included in *section 1.4.2.* (b) (4)			

Table 1 was reproduced from "__cdsesub1_evsprod_nda211340_0001_m3_32-body-data_32p-drug-prod_amlodipine-oralsusp_32p1-desc-comp_description-and-composition.pdf," located in Module 3.2.P.1

- **Description of container closure system –** 185 cc HDPE bottles with 28 mm (b) (4) (b) (4) caps and induction seal.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Antimicrobial Effectiveness Testing**
  Drug product is (b) (4) with (b) (4) The applicant states in 3.2.P.5.3.3 that the suitability of USP <51> for AET has been evaluated and confirmed for use, but the results of the testing cannot be located in the submission. This information will be requested via IR.

  R #1 Deficiency #1: **It is noted in 3.2.P.5.3.3 that you state USP <51> has been evaluated and confirmed for antimicrobial effectiveness testing (AET), but the AET results cannot be located in the submission. Please provide a detailed summary of the results of AET studies or provide the location in the application where this**

information is located; the AET studies should include data from at least one batch of product manufactured at or below the lowest acceptable concentration of the (b) (4) based on the label claim.

Applicant response: The applicant provided results from AET performed per USP <51> on two lots of drug product formulated at (b) (4) mg/mL and (b) (4) mg/mL of (b) (4) corresponding to (b) (4) and (b) (4) of the label claim, respectively. The (b) (4) mg/mL formulation met USP <51> acceptance criteria for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* and fungal organisms but failed to meet acceptance criteria for (b) (4) which showed a (b) (4) log reduction at Day 14 and a (b) (4) log increase at Day 28. The (b) (4) mg/mL (b) (4) % of label claim) formulation met all USP <51> acceptance criteria for all organisms.

Review of response: Adequate. The applicant has demonstrated antimicrobial effectiveness at the label claim of (b) (4) %.

Note to reviewer - The Chemistry reviewer alerted Microbiology to the fact that (b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: ***Adequate.***
Description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industrv: (b) (4)

(b) (4)

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

Reviewer's Assessment: ***Adequate.***

P.5 Control of Drug Product

(b) (4)

Reviewer's Assessment: ***Adequate.***
The proposed microbial limits and testing procedures comply with regulatory expectations.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Three development batches, 1 pilot batch and 3 registration batches of drug product were placed under long-term (5±3°C/ambient RH) and accelerated (25±2°/ambient RH) conditions in the upright position.

For the development batches, (b) (4) was tested at 0, 2, 4, 6, 8, 12, 25, 52, 78 and 104 weeks for long-term samples and at 0, 2, 4, 6, 8, 12 and 26 weeks for accelerated samples. No AET or microbial limits testing was performed. Testing is completed for the development batches.

For the pilot batch, microbial limits and (b) (4) (b) (4) were tested at 0, 3, 6 and 12 months for long-term samples and at 0, 3 and 6 months for accelerated samples. Testing is completed for the pilot batch.

For the registration batches (studies ongoing), microbial limits and (b) (4) (b) (4) are tested at 0, 6, 12, 24 and 36 months for long-term samples and at 0 and 6 months for accelerated samples.

Based on the completed stability studies for the development batches and the pilot batch as well as the currently available data for the registration batches, a shelf-life of 24 months has been proposed. The proposed shelf-life may be extended as additional stability data becomes available.

Note to Reviewer – AET will be conducted through the end of shelf-life on all 3 registration batches.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to placing the first 3 commercial lots of drug product on long-term and accelerated stability. Annually thereafter, 1 lot of drug product, if manufactured, will be placed on long-term and accelerated stability. Testing will be performed at 0, 3, 6, 12, 24 and 36 months for long-term samples and at 0, 3 and 6 months for accelerated samples. The 3-month testing point will only be used for the first 3 lots.

P.8.3 Stability Data

Through 12 months of stability testing for the registration batches, no excursions occurred for microbial limits or (b) (4).

R Regional Information

- **Executed Batch Records**
  Batch records are provided for batches 3144565R, 3144566R and 3144567R.

- **Comparability Protocols**

(b) (4)

Note to Reviewer – The applicant does not report any changes to the release/stability specifications associated with the alternate manufacturing facility.

Reviewer's Assessment: ***Adequate.***
The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

- **2.A. Package Insert**
  Drug product is labeled as a ready-to-use oral suspension to be stored at 2-8°C.

Reviewer's Assessment: ***Adequate.***

List of Deficiencies: (None)

Primary Microbiology Reviewer Name and Date: Jason M. God, Ph.D., 01/25/2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Denise A. Miller, Senior Microbiologist, 01/25/2019

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