

CLINICAL PHARMACOLOGY REVIEW

NDA Number	211340
Submission Date	09/14/2018
Submission Type	505(b)(2)
Generic name	Amlodipine Besylate
Brand name	Katerzia
Applicant	Silvergate Pharmaceuticals, Inc.
Dosage form	Oral Suspension
Strength	1 mg/mL
Drug Class	Calcium Channel Blocker
Associated IND	116485
OCP Division	Office of Clinical Pharmacology DCP-1
OND Division	Division of Cardiovascular and Renal Products (DCRP)
Primary Reviewer	Anusha Ande, PhD
Secondary Reviewer	Sudharshan Hariharan, PhD

Table of Contents

1. EXECUTIVE SUMMARY	2
1.1 Recommendations	2
1.2 Post-Marketing Requirements and Commitments	2
1.3 Summary of important clinical pharmacology and biopharmaceutics findings	2
2. QUESTION BASED REVIEW	3
2.1 General Attributes of the Drug Product	3
2.2 Specific Review Questions.....	5
3. APPENDICES.....	8
3.1 Pivotal Relative bioavailability study review.....	8

1. EXECUTIVE SUMMARY

Silvergate is seeking approval for Amlodipine Oral Suspension 1 mg/mL under the provisions of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The application relies on the Agency's previous findings of safety and effectiveness for the reference listed drug (RLD), Norvasc® (amlodipine) tablets approved as NDA 019787 in 1992. 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 is seeking approval for the following indications at the same doses as approved for Norvasc®:

- Treatment of hypertension in adults and children 6 years of age and older, to lower blood pressure
- 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%.

No additional clinical efficacy data is presented in this application and no new claims are being sought with this application.

The applicant has conducted two clinical pharmacology studies: 1) A pilot relative bioavailability (BA) study: open label, randomized, 2-way crossover study to evaluate the relative BA of single dose of 5 mg Amlodipine Oral Suspension compared to a single dose of Norvasc® 5 mg in 10 healthy subjects under fasted conditions; 2) A pivotal relative BA study to bridge Amlodipine Oral Suspension to Norvasc® tablets: open label, randomized, 3-way crossover study to assess the relative BA of single dose of 5 mg Amlodipine Oral Suspension compared to a single dose of Norvasc® 5 mg under fasted conditions in healthy subjects. Food-effect for single oral dose of 5 mg Amlodipine Oral Suspension was also assessed in the same study in another period.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 (OCP/DCP1) has reviewed the NDA submission. The results of the relative BA study support approval of Amlodipine Oral Suspension for the proposed indication at the doses as approved for the listed drug Norvasc®. The food effect results support administration of Amlodipine Oral Suspension with or without food. The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

1.2 Post-Marketing Requirements and Commitments

None.

1.3 Summary of important clinical pharmacology and biopharmaceutics findings

- The results of the pivotal relative BA study demonstrate that Amlodipine Oral Suspension, 1 mg/mL is bioequivalent to the RLD Norvasc® tablets under fasted conditions. The results of the relative BA study are summarized in **Table 3**.
- Amlodipine exposure was similar after administration of Amlodipine Oral Suspension under fed and fasted conditions indicating a lack of food effect for Amlodipine Oral

Suspension, 1 mg/mL, which is consistent with results reported for Norvasc® tablets. The food effect results are summarized in **Table 4**.

- The bioanalytical method used to measure amlodipine is validated and the performance of the method in the clinical studies is acceptable as per the specifications outlined in the *Bioanalytical Method Validation Guidance* (See **Table 2**).

2. QUESTION BASED REVIEW

This is an abridged version of the question-based review. For a detailed review of the clinical pharmacology of Norvasc®, refer to the original NDA 19,787.

2.1 General Attributes of the Drug Product

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 suspension, filled as 150 mL in 185-cc ^{(b)(4)} round white, opaque, high-density polyethylene bottles with ^{(b)(4)} ^{(u)(4)} child-resistant closures ^{(u)(4)}.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Amlodipine Oral Suspension contains the following inactive ingredients: Simethicone ^{(b)(4)}, ^{(b)(4)} Sodium benzoate, Citric acid ^{(b)(4)}, Sodium citrate ^{(b)(4)}, Sucralose, Silicon dioxide colloidal ^{(b)(4)}, Polysorbate 80, Hypromellose ^{(u)(4)}, Sodium hydroxide ^{(b)(4)}, ^{(b)(4)} and ^{(b)(4)} water.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

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. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle is dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro, but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa = 8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor-binding site, resulting in a gradual onset of effect.

Amlodipine 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 precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate-pressure product, and thus, myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

Proposed Indications

Amlodipine Oral Suspension is indicated for the treatment of hypertension in adult patients and pediatric patients 6 years of age and older to lower blood pressure. In adults, Amlodipine Oral Suspension is also indicated for the symptomatic treatment of chronic stable angina, treatment of confirmed or suspected vasospastic angina, and, in patients with recently documented coronary artery disease by angiography and without heart failure or an ejection fraction < 40%, Amlodipine Oral Suspension is indicated to reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure.

2.1.3 What are the proposed dose(s)?

The proposed doses are the same as those for the RLD Norvasc®.

The usual initial antihypertensive oral dose of Amlodipine Oral Suspension is 5 mg once daily, and the maximum dose is 10 mg once daily.

Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding Amlodipine Oral Suspension to other antihypertensive therapy.

Pediatric starting dose: 2.5 mg to 5 mg once daily in pediatric patients aged 6-17 years.

Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: The recommended dose for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Coronary artery disease: The recommended dose range for patients with coronary artery disease is 5–10 mg once daily. In clinical studies, the majority of patients required 10 mg.

2.2 Specific Review Questions

2.2.1 What are the design features of clinical pharmacology studies used to support dosing or label claims?

The applicant submitted two clinical pharmacology studies (**Table 1**): 1) The pilot relative bioavailability study (SG05-01) compared the bioavailability of amlodipine from 5 mg Amlodipine Oral Suspension, 1 mg/mL and 5 mg Norvasc® tablet following single oral dose administration in 10 healthy subjects under fasted conditions; 2) The pivotal relative bioavailability study (SG05-02) compared the bioavailability of amlodipine from 5 mg Amlodipine Oral Suspension (Treatment A), 1 mg/mL and 5 mg Norvasc® tablet (Treatment B) following single oral dose administration in healthy subjects under fasted conditions. Food-effect for single oral dose of 5 mg Amlodipine Oral suspension (Treatment C) was also assessed in the same study in another period under fed conditions.

Table 1. Summary of clinical pharmacology studies

Study	Type	Design	Study participants
SG05-01	Pilot Relative Bioavailability study	Open label, randomized, two-period, two-treatment, crossover, single oral dose comparative bioavailability study in healthy adults under fasted state administration	Enrolled: 10 (3 men and 7 women) Completed: 10 (3 men and 7 women) Age Range: 25-55 years
SG05-02	Pivotal Relative Bioavailability study	Open-label, randomized, three-period, three-treatment crossover study to assess the relative bioavailability of a test formulation of a single 5 mg dose of amlodipine oral suspension, 1 mg/mL, under fasted (Treatment A) and fed conditions (Treatment C) versus Norvasc® (Treatment B) 5 mg tablets under fasted conditions in healthy adults	Enrolled: 24 (14 men and 10 women) Completed: 22 (13 men and 9 women) Age Range: 23-55 years

Source: Clinical Study Reports of Study No. SG05-01 and SG05-02

2.2.2 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

A validated LC-MS/MS analytical method for determining amlodipine in human plasma treated with K₃EDTA was used for the bioanalysis of this study. Amlodipine-d₄ maleic salt was used as

the internal standard (IS) for amlodipine. Human plasma containing amlodipine, and the internal standard, amlodipine-D4, was extracted with an organic solvent mixture. Following centrifugation, transfer of the organic layer, and evaporation, an aliquot of the reconstituted extract was injected onto a ^{(b) (4)} LC-MS-MS equipped with an HPLC column. The peak area of the m/z 409 → 238 amlodipine product ion was measured against the peak area of the m/z 413 → 238 amlodipine-D4 internal standard product ion. Calibration curve was found to be linear from 0.25 ng/mL to 25 ng/mL. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLOQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Greater than two-thirds of the incurred samples concentration results were within 20% of the original concentration of the respective samples, thus meeting the acceptance criteria for incurred samples reanalysis.

Analytical methods were validated and performed within acceptable limits as shown in **Table 2**.

Table 2. Summary of bioanalytical sample analysis and method validation

Analyte	Amlodipine
Method	LC-MS/MS
Internal Standard	Amlodipine-d4 maleic salt
Matrix	Human K ₃ EDTA Plasma
Extraction	Liquid-Liquid Extraction
LLOQ (ng/mL)	0.25
CCs (ng/mL)	0.25, 0.5, 1.25, 2.5, 5, 10, 22.5, 25
QCs (ng/mL)	LQC – 0.75 MQC – 8 HQC – 18.8
Accuracy	
Inter- run Accuracy (% Bias)	-0.5 to -0.3
Intra- run Accuracy (% Bias)	-7.2 to -1.8
Precision	
Inter- run Precision (%CV)	5.2 to 9.5
Intra- run precision (%CV)	2.8 to 4.2
Average Recovery%	
Amlodipine	77.8 to 110.3
Amlodipine-d4 maleic salt	97.2

CCs: Calibration Curve standards, QCs: Quality Control Samples, LLOQ: Lower Limit of Quantification

Source: Method validation and analytical reports (bioanalyt-analyt-met_study-4003734_bioanalytical-report.pdf, bioanalyt-analyt-met_study-4003734_analytical-validation-report)

2.2.3 What is the relative bioavailability of Amlodipine Oral Suspension compared to Norvasc® tablets?

The geometric mean ratios along with its 90% confidence interval (CI) of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for 5 mg Amlodipine Oral Suspension compared to Norvasc® tablets from pivotal study SG05-02 are summarized in **Table 3**.

Table 3. Relative bioavailability assessment results

Parameter	Geometric Least Squares Mean		T/R Ratio (%)	T/R 90% CI
	T (N=22)	R (N=22)		
$\ln(C_{max})$ (ng/mL)	2.6	2.6	100.3	95.3 – 105.5
$\ln(AUC_{0-t})$ (h*ng/mL)	127.5	126.4	100.9	94.9 – 107.4
$\ln(AUC_{0-\infty})$ (h*ng/mL)	149.7	150.2	99.7	94.4 – 105.2

T: Amlodipine Oral Suspension, 1 mg/mL, R: Norvasc® 5 mg tablets

Source: Clinical Study Report of Study SG05-02

The test formulation of 5 mg amlodipine oral suspension, 1 mg/mL (Silvergate Pharmaceuticals, Inc.) is bioequivalent to the RLD Norvasc® 5 mg tablets (Pfizer Labs), under fasted conditions. The study results from the pilot study SG05-01 also demonstrate bioequivalence between the two products under fasted conditions.

2.2.4 What is the effect of food on the bioavailability of the drug from the drug product?

The geometric mean ratios along with its 90% confidence interval (CI) of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for administration of 5 mg Amlodipine Oral Suspension with high-fat, high-calorie breakfast compared to fasted state administration are summarized in **Table 4**.

Table 4. Food effect assessment results

Parameter	Geometric Least Squares Mean		Fed/Fasted Ratio (%)	Fed/Fasted 90% CI
	Fed	Fasted		
ln(C _{max}) (ng/mL)	2.4	2.6	91	86.4 – 95.9
ln(AUC _{0-t}) (h*ng/mL)	129.7	127.5	101.7	95.5 – 108.4
ln(AUC _{0-∞}) (h*ng/mL)	151.4	149.7	101.2	95.8 – 106.9

Source: Clinical Study Report of Study SG05-02

Amlodipine exposure was similar after administration of the Amlodipine Oral Suspension under fed and fasted conditions indicating a lack of food effect for the Amlodipine Oral Suspension, 1 mg/mL, which is consistent with results reported for Norvasc® tablets. The study results support administration of Amlodipine Oral Suspension without regards to meal.

3. APPENDICES

3.1 Pivotal Relative Bioavailability Study Review

Study No: SG05-02	EDR: \\cdsesub1\evsprod\nda211340\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\study-sq05-02\report-body.pdf
Study Date: September 23, 2017 to October 28, 2017	
Title of Study: 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.	
Investigational Products: Test Product (T) Amlodipine Oral Suspension, 1 mg/mL Reference (R) Norvasc® (Amlodipine) 5 mg tablet	
Study: <ul style="list-style-type: none"> • Design: Open label, randomized, 3-way, crossover study with 3 dosing periods: <ul style="list-style-type: none"> ○ A single 5 mg dose of Amlodipine Oral Suspension, 1 mg/mL, under fasted conditions (Treatment A) ○ A single dose of 5 mg Norvasc® tablet under fasted conditions (Treatment B) ○ A single 5 mg dose of Amlodipine Oral Suspension, 1 mg/mL, under fed conditions (Treatment C) • Washout: There was a 2-week washout period between each of the dosing periods. • Study participants: 22 healthy adults (13 men and 9 women), 23- 55 years of age. 	

- **Treatments Administered**

Amlodipine Oral Suspension:

Each subject received the 5 mg dose of amlodipine oral suspension, 1mg/mL (dose = 1 x 5mL) via an oral dosing syringe, followed by 240 mL of room temperature tap water. Clinic staff administered the dose from the oral syringe directly in to the subject’s mouth. Subjects formed a tight seal with lips around the tip of the syringe and swallowed the dose as it was pushed into mouth. Using the 240 mL dosing water, clinical staff drew up 5 mL of water into the empty oral dose syringe and administered the rinse to the subject. This procedure was repeated for a total of 2 x 5 mL water rinses. The subjects were instructed to drink the remaining 230 mL of water in the cup. A mouth check was performed immediately after dosing to ensure that the medication had been appropriately swallowed.

Norvasc® (amlodipine) Tablet:

A single dose of Norvasc® 5 mg tablet was administered with 240 mL of room temperature tap water. Subjects swallowed the intact tablet.

- **Sampling times (h):** pre-dose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10,12, 14, 24, 48, 72, 96, 120, 144, and 168 h post-dose.

Pharmacokinetic (PK) parameters calculated: AUC_{0-t}, AUC_{0-∞}, C_{max}, T_{max}, AUC_{Extrap} (%), C_{last}, T_{last}, t_{1/2}, and K_{el}

Analytical Method:

- A validated LC-MS method, as described in section 2.2.2, was used for the estimation of amlodipine in human K₃EDTA plasma using amlodipine-d4 maleic salt as internal Standard.
- The analytical range for amlodipine in plasma was 0.25 ng/mL - 25 ng/mL

Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical Methods:

The natural logarithmic transformed pharmacokinetic exposure parameters (AUC_{0-∞}, AUC_{0-t}, and C_{max}) were analyzed for differences between treatments using an ANOVA. The statistical model included factors for sequence, subject within sequence, treatment, and period and subject as the random effect. The 90% confidence interval for the ratio of the geometric means of the test product and the reference listed drug (Treatment A/Treatment B) was calculated for each parameter. Additionally, the impact of food on amlodipine exposure was assessed (Treatment C/Treatment A).

Results:

22 subjects completed the study. A total of 1320 blood samples were collected for analysis of plasma amlodipine concentrations.

Table 1. Demographics

Age range	23 - 55 years
Males	13 (59.1%)
Females	9 (40.9%)
Weight	52.9 – 100.1 kg

Source: Clinical Study Report Study SG05-02

Table 2. Subject Disposition

	All subjects N (%)
Randomized	24 (100)
Completed	22 (91.7)
Not Completed	2 (8.3)
Protocol Deviation	1 (50)
Lost to Follow-up	1 (50)

Source: Clinical Study Report Study SG05-02

Two subjects did not complete the study as one subject was withdrawn by the Investigator due to a protocol non-compliance of positive urine pregnancy test on Day 14 after dosing with Treatment B and another subject was lost to follow-up on Day 6 after dosing with Treatment A in Period 1.

For Statistical Summary of relative BA data, refer to **Table 3** in section 2.2.3 and comparison of fed and fasted state, refer to **Table 4** in section 2.2.4

Table 3. Summary of PK Parameters

Parameter	Treatment A Arithmetic Mean (SD) (N=22)	Treatment B Arithmetic Mean (SD) (N=22)	Treatment C Arithmetic Mean (SD) (N=22)
C _{max} (ng/mL)	2.7 (0.8)	2.8 (0.9)	2.4 (0.7)
AUC _{0-t} (ng.hr/mL)	139.1 (51.6)	139.4 (58.9)	136.9 (49.9)
AUC _{0-∞} (ng.hr/mL)	162 (59.2)	163.4 (66.9)	160.3 (61.2)
T _{max} (hr)	7.8 (1.9)	7.7 (1.8)	10.2 (2.9)
t _{1/2} (hr)	46 (13.5)	48.4 (14.8)	46.9 (14.2)
AUC _{Extrap} (%)	14.8 (5.1)	15.8 (6.5)	14.5 (4)

Source: Clinical Study Report Study SG05-02

Treatment A: Amlodipine Oral Suspension-Fasted, Treatment B: Norvasc® Tablet, Treatment C: Amlodipine Oral Suspension-Fed

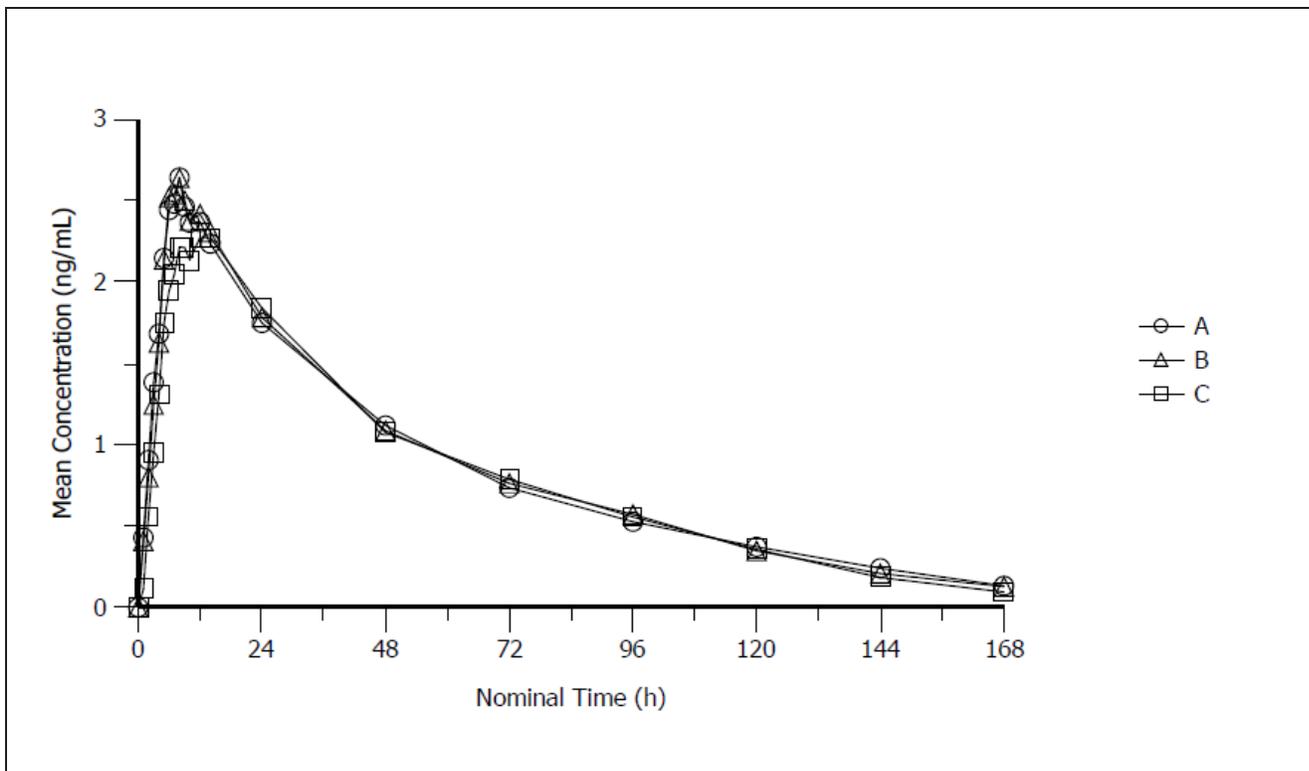


Figure 1: Plot of mean plasma amlodipine concentration vs time profiles (A: Amlodipine Oral Suspension-Fasted, B: Norvasc® Tablet, C: Amlodipine Oral Suspension-Fed)
 Source: Clinical Study Report Study SG05-02

Conclusions:

The study results demonstrate bioequivalence between the Amlodipine Oral Suspension and Norvasc® tablet under fasted conditions and no food effect was observed for Amlodipine Oral Suspension.

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/

ANUSHA ANDE
06/04/2019 02:14:27 PM

SUDHARSHAN HARIHARAN
06/04/2019 02:28:49 PM