OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 219531	Submission Date(s): 09/24/2024
Brand Name	SDAMLO
Generic Name	Amlodipine besylate
Clinical Pharmacology Reviewer	Ritika Kurian, PhD
Clinical Pharmacology Team Leader	Elly Moon, PharmD
OCP Division	Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
OND Division	Division of Cardiology and Nephrology (DCN)
Sponsor	Brillian Pharma, Inc.
Submission Type; Code	505(b)(2); Original-1
Formulation; Strength(s)	2.5 mg, 5 mg and 10 mg freeze-dried powder for oral solution
Indication	Treatment of hypertension and coronary artery disease (Chronic Stable Angina, Vasospastic Angina (Prinzmetal's or Variant Angina), Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40%)

1. Executive Summary

Brillian Pharma Inc. submitted a 505(b)(2) new drug application (NDA) for SDAMLO (amlodipine oral solution), 2.5 mg, 5 mg, and 10 mg indicated for the treatment of hypertension and coronary artery diseases (CADs) in adults and children 6 to 17 years of age. The proposed product is an age-appropriate formulation of amlodipine intended to serve patient population with difficulty of swallowing traditional tablet or capsule oral solid dosage forms. The active pharmaceutical ingredient (API) in the product is amlodipine besylate.

For the 505(b)(2) regulatory pathway, the Applicant is relying on the FDA's finding of safety and effectiveness for the proposed listed drug (LD) Norvasc® (NDA 019787 by Pfizer Laboratories). The Applicant conducted a single relative bioavailability and food effect study of amlodipine oral solution and Norvasc® (ARL/22/073) to demonstrate comparative bioavailability and thereby, providing a scientific bridge of the proposed product to Norvasc®.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology information submitted for NDA 219531. We find that the current application is acceptable for approval from the clinical pharmacology standpoints.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The key clinical pharmacology findings are as follows:

- Based on the study ARL/22/073, the total systemic exposure (AUC) of amlodipine oral solution 5mg and reference product Norvasc 5 mg tablets, is considered comparable under fasting conditions.

- Absence of food effect was concluded as 90% confidence intervals of geometric mean ratio of C_{max}, AUC_{0-t} and AUC_{0-inf} for amlodipine under fasting and fed conditions were within the acceptance range of 80.00% to 125.00%.

2. QBR

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of SDAMLO (amlodipine besylate freeze-dried powder for oral solution)?

In an IND meeting (IND #157136) held between the Applicant and FDA, the Applicant requested for feedback on the suitability of the 505(b)(2) pathway and their drug development program to support the NDA. During this meeting, clinical pharmacology review team recommended that the Applicant use the 10 mg dosage form instead of 5 mg for the pivotal bioavailability (BA) study (reference ID: 5086459). Despite the recommendation, the Applicant conducted a relative bioavailability study using 5 mg strengths of amlodipine oral solution and Norvasc® and is seeking a waiver for in vivo BA study for the 10 mg and 2.5 mg strength. This biowaiver request will be reviewed by the biopharmaceutics review team.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What general clinical pharmacology features of amlodipine besylate are relevant to the current submission?

For details of the clinical pharmacology features of amlodipine besylate, please refer to the labeling of amlodipine besylate tablets (NDA 019787).

2.2.2 Is the SDAMLO appropriately bridged to the amlodipine besylate formulation of the listed drug?

To support bridging of SDAMLO to Norvasc®, the Applicant provided PK data from a relative bioavailability study (ARL/22/073) conducted between the proposed product and the listed drug.

The current section will focus on the relative bioavailability of amlodipine oral solution 5mg versus Norvasc 5 mg tablets based on the relative BA study ARR/22/073. The results demonstrate that the systemic exposure of amlodipine is similar between the SDAMLO and Norvasc® under fasting conditions.

2.2.2.1 Study ARL/22/073

Study design

The study was a randomized, open label, balanced, three treatment, three period, three sequence, single dose, crossover bioequivalence study to assess the relative bioavailability of amlodipine freeze-dried powder for oral solution 5mg (FD-POS, in a unit-dose container) under fasting condition (T1, Treatment A) and fed conditions (T2, Treatment C) versus reference product (R, Treatment B) Norvasc (amlodipine besylate) 5 mg tablets in healthy adult male and female subjects. Subjects underwent

screening evaluations to determine eligibility within 21 days prior to dosing of Period-I. Subjects were randomized to receive single oral dose (1 x 5 mg FD-POS bottle) of the test product (T) and (1 x 5 mg Tablet) of reference product (R) as per randomization with 240 ± 2 mL of water at ambient temperature under fasting (T1) and fed (T2) conditions. A washout period of 21 days between period-I and period-II and period-II and period-III was maintained in the study.

For the fasting study, the subjects were administered the investigational product after an overnight fast of at least 10 hrs.

Blood samples were collected at pre-dose (collected within 1 hour prior to dosing) and up to 144 hours post-dose in each period.

PK results

A total of 23 subjects completed the study and samples of 24 subjects were analyzed. The data of 19 subjects (except subject number (b) (6)) were considered for statistical analysis between test T1 (fast) and reference (R). Subject (b) (6) dropped out of from period-II due to personal reasons and was withdrawn from period-III due to protocol non-compliance. Subjects (b) (6) withdrew from the study due to adverse event including vomiting and fever.

The mean plasma amlodipine concentration versus time profile is provided in Figure 1. Summary of PK parameters and statistical comparison of amlodipine powder for oral solution to amlodipine tablet is provided in Table 1. These listed findings were reanalyzed and confirmed by the clinical pharmacology reviewer.

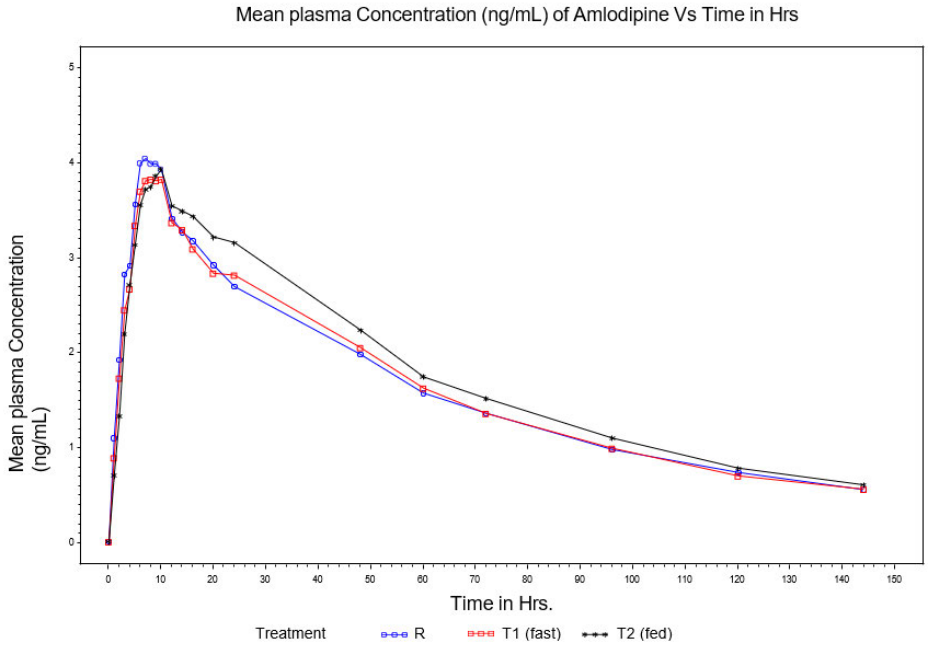

Figure 1 Mean Plasma Amlodipine Concentration-Time Plots
Abbreviations: R=reference; T1(fast)=test under fast; T2(fed)=test under fed.
Source: Applicant's analysis. Study ARL/22/073 CSR figure 01, page 95 of 103

Table 1 Summary of PK parameters and statistical assessment of bioavailability between amlodipine powder for oral solution and amlodipine tablet administration

Parameters	Geometric LSM		T1/R Ratio(%) (90% Confidence Interval)	BIOEQUIV	Intra CV	Power
	Treatment T1	Treatment R	T1 vs R	-	(%)	%
Cmax (ng*hr/mL)	3.9267	4.2399	92.6119 (87.9349, 97.5375)	YES	9.3805	99.9995
AUC0-t (ng*hr/mL)	208.7985	224.1649	93.1450 (88.6244, 97.8962)	YES	9.0069	99.9998
AUC0-inf (ng/mL)	241.5979	264.9088	91.2004 (86.3379, 96.3367)	YES	9.9238	99.9984
Acceptance Criteria for Primary Parameters: 80.00%-125.00%						

Abbreviations: AUC_{inf}=area under the concentration versus time curve from time 0 to infinity; AUC_{last}=area under the concentration versus time curve from time 0 to the last measurable plasma concentration; C_{max}=maximum plasma concentration; CV, coefficient of variation; LSM=least squares mean.
Note: Test = amlodipine powder for oral solution; Reference = amlodipine tablet.
Source: Applicant's analysis. Study ARL/22/073 CSR Table 01 (B), page 15 of 103

2.2.3 Does food affect the pharmacokinetics of amlodipine freeze-dried powder for oral solution?

The sponsor evaluated the impact of high-fat and high-calories breakfast (approximately 800-1000 kilocalories) on the bioavailability of amlodipine oral solution. On dosing day, after an overnight fast of at least 10 hours, all subjects were given high-fat, high calorie meal in 30 minutes or less; 30 minutes prior to drug administration. Blood samples were collected at pre-dose (collected within 1 hour prior to dosing) and up to 144 hours post-dose in each study period.

PK results

The data of 18 subjects (except subject number (b) (6)) were considered for statistical analysis. Subject number (b) (6) was withdrawn before dosing of period-I due to a health-related event (vomiting). Subject number (b) (6) dropped out before period-II due to personal reason and subject number (b) (6) was withdrawn from period-III due to protocol non-compliance (urine for DOA positive for THC).

Blood samples were collected at pre-dose (collected within 1 hour prior to dosing) and up to 144 hours post-dose in each study period.

The mean plasma amlodipine concentration versus time profile is provided in Figure 1. Summary of PK parameters and statistical comparison of amlodipine oral solution under fasted and fed condition is provided in Table 2. These listed findings were reanalyzed and confirmed by the clinical pharmacology reviewer.

Table 2 Summary of PK parameters and statistical assessment of bioavailability between amlodipine powder for oral solution under fasted (T1) and fed (T2) conditions

Parameters	Geometric LSM		T1/T2 Ratio(%) (90% Confidence Interval)	BIOEQUIV	Intra CV	Power
	Treatment T1	Treatment T2	T1 vs T2	-	(%)	%
Cmax (ng*hr/mL)	4.0060	4.0918	97.9026 (90.8109, 100.5347)	YES	9.4033	99.9998
AUC0-t (ng*hr/mL)	217.0373	234.6482	92.4948 97.1365, 108.3336)	YES	10.0689	99.9989
AUC0-inf (ng/mL)	255.3194	271.1322	94.1679 (93.5081, 106.0234)	YES	11.6001	99.9833
Acceptance Criteria for Primary Parameters: 80.00%-125.00%						

Abbreviations: AUC_{inf}=area under the concentration versus time curve from time 0 to infinity; AUC_{last}=area under the concentration versus time curve from time 0 to the last measurable plasma concentration; C_{max}=maximum plasma concentration; CV, coefficient of variation; LSM=least squares mean.
Note: Test = amlodipine powder for oral solution; Reference = amlodipine tablet.
Source: Applicant's analysis. Study ARL/22/073 CSR Table 01 (C), page 16 of 103

2.3 ANALYTICAL SECTION

The concentrations of amlodipine in human plasma samples from study ARL/22/073 were determined by a validated HPLC method using MS/MS detection. The details of the bioanalytical method adopted for the quantitative analysis of the plasma samples are summarized in Table 3.

Table 3 Summary of Bioanalytical Method

API	Amlodipine
Method	LC-MS/MS
Sample Matrix	Human plasma
Validated Method	(b) (4) /MET/MI/602ADP
Internal Standard	Amlodipine-D4
Laboratory Name	(b) (4)
LLOQ (ng/mL)	0.050
ULOQ (ng/mL)	9.983
Concentration/Validation range (ng/mL)	0.050-9.983
QC (ng/mL)	0.150, 1.250, 3.501, 8.003, 40.014
Accuracy (bias, %)	97.4% to 101.7%
Precision (%)	1.29% to 3.96%

Incurred Sample Reanalysis (ISR) within acceptance criteria (± 20%)	99.3% (136 out of 137)
Analyte Stability When Stored at -80° C (Days)	105
Samples collection & analysis time	Date of sample receipt: 02/18/2023 Total samples received/analyzed: 1386 Date of first sample analysis: 03/17/2023 Date of last sample analysis: 03/25/2023
Abbreviations	LLOQ Lower Limit of Quantification; ULOQ Upper Limit of Quantification

Source: Applicant's bioanalytical report 01 (module 5.3.14)

2.4 OFFICE OF STUDY INTEGRITY AND SURVEILLANCE (OSIS) INSPECTION REPORT

OSIS determined that an inspection was not needed for the bioanalytical and clinical sites (b) (4). The OSIS conducted a Remote Regulatory Assessment (RRA) for the bioanalytical site in (b) (4) and concluded that data from the reviewed studies were reliable. The clinical site was previously inspected by the Office of Inspections and Investigations (OII) in March 2025 and OSIS concluded that the findings did not impact data integrity or subject safety and that the data were reliable.

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