CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-026

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22-026	Submission Date(s):	January 31, 2006 June 8, 2006
Generic Name	Amlodipine Besylate	
Reviewer	Carol Noory	
Team Leader	Patrick Marroum	
OCPB Division	Division of Clinical Pharmacology I	
ORM division	Cardiovascular-Renal Products	
Sponsor	Synthon Pharmaceuticals, Inc.	
Submission Type; Code	505(b)2	
Formulation; Strength(s)	2.5 mg, 5 mg, 10 mg Orally Disintegrating Tablets	
Indication	Treatment of hypertension and chronic stable vasospastic angina	

1. Executive Summary

Amlodipine is used clinically for the treatment of hypertension; for the symptomatic treatment of chronic stable angina; and for the treatment of confirmed or suspected vasospastic angina. It may be used alone or in combination with other antihypertensive agents. Synthon Pharmaceuticals Inc. has developed a new orally disintegrating tablet that provides a pharmaceutical alternative to NORVASC® immediate-release conventional tablets manufactured by Pfizer. The sponsor proposes to market the tablets in strengths of 2.5 mg, 5 mg, and 10 mg which are formulated to be bioequivalent to the reference listed drug, NORVASC® (NDA 019-787) which is manufactured

by Pfizer, Inc. The amlodipine besylate orally disintegrating tablets (ODTs) are formulated to disintegrate once exposed to fluid, such as saliva. The tablets are designed to be easily swallowed in order to provide the patient with a dosage form of amlodipine that is easier to take, especially for adolescent patients (ages 6-17 years) and the elderly, who have traditionally had difficulties swallowing more conventional dosage forms.

This application includes no clinical trials; however, the bioequivalence and clinical safety of amlodipine orally disintegrating tablets were investigated in a single-dose in vivo study conducted in healthy subjects comparing the 10 mg amlodipine orally disintegrating tablet (ODT) administered without water to a 10 mg NORVASC® tablet administered with water. A food-effect study was conducted to determine the effect of food on amlodipine ODTs compared to NORVASC® tablets using the 10 mg product. The sponsor is relying on the Agency's findings of safety and efficacy for NORVASC® Tablets, USP, originally approved in 1992. The firm proposed a suitable dissolution procedure. Dissolution profiles using the sponsor's proposed method were evaluated for the 2.5 mg and 5 mg orally disintegrating tablets compared to the 10 mg orally disintegrating tablets used in the bioavailability studies (biolot). This data was used to support a biowaiver for the 2.5-mg and 5-mg strength tablets. The dissolution of the 10 mg NORVASC® tablets was determined using the approved method for that product. Literature was submitted to support the clinical pharmacology portion of the labeling. Linear relationships were found between the dose and the plasma levels of amlodipine.

The following clinical pharmacology and biopharmaceutic's information was submitted in this application:

1. The firm conducted a bioequivalence study under fasting conditions comparing the highest proposed strength (10 mg) of amlodipine orally disintegrating tablet to the approved 10-mg NORVASC® tablet reference product manufactured by Pfizer (Study CSP.US01.ADP.odt10.001/ CPA 235-05).
2. A food effect study was conducted comparing the effect of food on the bioavailability of the amlodipine orally disintegrating tablet to NORVASC® tablet using the 10 mg product (Study CSP.US01.ADP.odt10.002/ CPA 236-05).
3. A waiver for the lower strength 2.5-mg and 5.0-mg strength ODTs was requested based on formulation proportionality, linear pharmacokinetics and similarity of the dissolution profiles compared to the 10-mg amlodipine orally disintegrating tablet (biolot) using a single dissolution procedure.
4. A waiver for pediatric studies was requested.
5. The sponsor's selected a dissolution method that is similar to the method used for Norvasc®. The paddle speed has been reduced due to the rapid dissolution of the product. The media and apparatus used are the same.
6. The sponsor has proposed a disintegration test (USP <701>) to the drug product regulatory specifications for release and stability.
7. The sponsor developed an acceptable analytical method to determine the level of amlodipine in human plasma.
8. The sponsor's labeling reflects the differences between their product and Norvasc®.
9. A DSI inspection of the study sites for study CPA 235-05 and CPA 236-05 was conducted.

Comments

1. FASTING STUDY: A significant difference was observed for Tmax between the TEST and the REFERENCE treatments according to Wilcoxon and median non-parametric tests and ANOVA. The mean of Tmax was 11.09 hours (6 hours – 32 hours) for the Test formulation and 7.17 hours (4 hours – 12 hours) for the Reference formulation. The sponsor needs to address this difference in Tmax for this orally disintegrating product.

2. WAIVER FOR LOWER STRENGTHS: A waiver for the lower strength 2.5-mg and 5.0-mg strength ODTs was requested based on formulation proportionality and similarity of the dissolution profiles compared to the 10-mg amlodipine orally disintegrating tablet (biolot) using a single dissolution procedure. The sponsor needs to provide additional dissolution data to support the biowaiver request. Dissolution data should be obtained on a minimum of 12 individual units of each strength, 2.5-mg and 5-mg ODTs, compared to the 10 mg ODT biolot drug. The proposed dissolution method can be used with three media covering the physiological pH range (i.e.; pH 1.2, 4.5 and 6.8). The information using 0.01N HCl submitted with the current application can be substituted for the pH 1.2 medium. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product. Individual data, mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included. Similarity in dissolution profiles between the test and reference products in each of the three media, using the f2 metric, should be determined. This information is discussed in the FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations" which is available on the CDER website.
3. DISSOLUTION SPECIFICATION: The sponsor's proposed dissolution method is acceptable; however, the specification proposed is not acceptable. Based on the data provided, the dissolution specification needs to be Q ——in 15 minutes. b(4)
4. BIOEQUIVALENCE STUDIES: The Division of Scientific Investigations' audit of the study sites for study CPA 235.05 and CPA 236-05 revealed deficiencies in the accuracy of drug treatment administration, dosing times, and pharmacokinetic blood sampling times. The inspection results are significant enough to compromise the integrity of the bioequivalence study. The data from the studies are inconclusive pending an acceptable resolution of these deficiencies.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed NDA 22-026. Approval of the clinical pharmacology and biopharmaceutics information cannot be made until the deficiencies cited in the DSI audit are addressed and resolved. In addition, the sponsor should appropriately addresses the following comments:

1. A significant difference was observed for Tmax between the TEST and the REFERENCE treatments according to Wilcoxon and median non-parametric tests and ANOVA. The mean of Tmax was 11.09 hours (6 hours – 32 hours) for the Test formulation and 7.17 hours (4 hours – 12 hours) for the Reference formulation. The sponsor needs to submit information to address this difference in Tmax.
2. The waiver requested for the lower strengths, 2.5-mg and 5.0-mg strength ODTs, is not granted. The sponsor should submit additional dissolution data to support the biowaiver requested. Dissolution data should be obtained on a minimum of 12 individual units of each strength, 2.5-mg and 5-mg ODTs, and compared to the 10 mg ODT biolot. The proposed dissolution method can be used with three media covering the physiological pH range (i.e.; pH 1.2, 4.5 and 6.8). The information using 0.01N HCl submitted with the current application can be substituted for the pH 1.2 medium. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product. Individual data, mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included. Similarity in dissolution profiles

between the test and reference products in each of the three media, using the f2 metric, should be determined.

The sponsor's proposed labeling for the "Clinical Pharmacology Section" and dissolution method are acceptable. After evaluation of the dissolution data submitted, the dissolution specification should be tightened. The following dissolution method and specification is recommended.

USP Apparatus 2:	Paddle Method
Rotation speed:	50 rpm
Volume:	500 mL
Medium:	0.01 M HCl
Tolerance:	Q ——— in 15 minutes

b(4)

The above comments should be forwarded to the firm.

An OCPB briefing was held on September 20, 2006. The attendees were Thomas Marcinak, Tapash Ghosh, Mehul Mehta, Patrick Marroum and Carol Noory.

1.2 PHASE IV COMMITMENTS: NONE

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Amlodipine is a vasoselective, dihydropyridine, calcium antagonist approved for the treatment of hypertension and angina pectoris. NORVASC® was approved by the FDA on July 31, 1992 under NDA 19-787. Synthon has developed a new orally disintegrating tablet dosage form of amlodipine that provides a pharmaceutical alternative to the currently approved conventional tablet formulation. Synthon Pharmaceuticals proposes to market the orally disintegrating tablets in 2.5-mg, 5-mg, and 10 mg strengths, which are formulated to be bioequivalent to NORVASC® Tablets manufactured by Pfizer.

The current application includes no clinical trials. The clinical efficacy and safety of the drug are based on the clinical information from the original NDA for NORVASC® Tablets, USP (NDA 019787). The submission contains the following information:

I. Bioequivalence studies

a. Study CPA 235-05-Fasting Study: A Randomized, Two-Period, Crossover, Single-dose, Bioequivalence Study on Amlodipine 10 mg ODT (Synthon Pharmaceuticals, Inc., USA) Versus NORVASC® 10 mg Tablets (Pfizer, Inc. USA) in Healthy Volunteers Under Fasting Conditions.

- ***Pharmacokinetics:***
  1. Based on the statistical results for amlodipine, the 90% confidence intervals for AUC0-t, AUC 0-inf and Cmax of the test compared to the reference formulation were found to be within the range of 80% -125%. The confidence intervals for AUC0-t, AUC0-inf, and Cmax were [95.44-104.00%], [95.47-103.93%], and [87.63-96.03%], respectively.
  2. The ratio of the geometric least square means for AUC0-t, AUC0-inf, and Cmax are 1.0, 1.0 and 0.9, respectively.
  3. A significant difference was observed for Tmax between the two treatments according to Wilcoxon and median non-parametric tests and ANOVA. The mean of Tmax was 11.09 hours for the Test formulation and 7.17 hours for the Reference formulation.
  4. Difference between the two treatments for Kel and t ½ were not significant at the 5% level according to ANOVA, Wilcoxon and median non-parametric tests.
  5. The total exposure to amlodipine was similar between the two treatments.
- ***Safety:*** There were no serious adverse events reported. No significant safety concerns were raised.

b. Study CPA 236-05: A Randomized, Two-Period, Crossover, Single-dose, Bioequivalence Study on Amlodipine 10 mg ODT (Synthon Pharmaceuticals, Inc., USA) Versus NORVASC® 10 mg Tablets (Pfizer, Inc., USA) in Healthy Volunteers Under Non-Fasting Conditions.

- ***Pharmacokinetics:***
  1. Based on the statistical results for Amlodipine, the 90% confidence intervals for AUC0-t, AUC 0-inf and Cmax of the test compared to the reference formulation was found to be within the range of 80% -125%. The confidence interval are

[93.38% to 99.87%] for $AUC_{(0-t)}$; [92.79% to 99.66%] for $AUC_{(0-\infty)}$; and [89.21-96.73%] for Cmax.

2. The ratio of the geometric least square means for AUC0-t, AUC0-inf, and Cmax are 1.0, 1.0 and 0.9, respectively.
3. A significant difference at the 5% significance was found between the Cmax (Test=3.42-7.72 ng/mL; Reference = 3.229-10.369 ng/mL) and the ln(Cmax)(Test = 1.23-2.04 ng/mL; Reference = 1.17-2.34 ng/mL) of the two treatments according to ANOVA analysis.
4. The mean of Tmax was 9.88 hours (3-12 hours) for the Test formulation and 8.08 hours (3-12 hours) for the Reference formulation. A significant difference was observed for Tmax between the two treatments according to Wilcoxon, median non-parametric tests and ANOVA.
5. The mean of Kel was 0.0164 hours-1 for the Test formulation and 0.155 hours-1 for the Reference formulation, while mean t ½ value was 44.54 and 48.60 hours following the same order. The coefficient of variation of Kel was approximately 22% and 26% for the Test and Reference formulations, respectively. Difference between the two treatments for Kel and t ½ according were not significant at 5% level to ANOVA, Wilcoxon and median non-parametric tests

- S*afety:* There were no serious adverse events reported. No significant safety concerns were raised.

2. Literature Study

The Amlodipine 505(b)(2) NDA clinical information is supported by way of reference to the approved NDA for NORVASC™ (N-019787)) and certain pertinent literature regarding the use of amlodipine in the treatment of hypertension. Sixty-eight references (68) were submitted in support of the NDA.

3. Waiver Requests

a. **Waiver for a biostudy of the 2.5-mg and 5.0-mg tablets.** A biowaiver was requested for the lower strengths based on linear kinetics, formulation proportionality and the in vitro dissolution comparison, which were similar using the dissolution procedure selected. The FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" states that "Waiver of *in vivo* BE studies for different strengths of a drug product can be granted under § 320.22(d)(2) when (1) the drug product is in the same dosage form, but in a different strength; (2) this different strength is *proportionally similar* in its active and inactive ingredients to the strength of the product for which the same manufacturer has conducted an appropriate *in vivo* study; and (3) the new strength meets an appropriate *in vitro* dissolution test. The guidance further states that "We (the Agency) recommend that a dissolution profile be generated for all strengths. If an appropriate dissolution method has been established, and the dissolution results indicate that the dissolution characteristics of the product are not dependent on the product strength, then dissolution profiles in one medium are usually sufficient to support waivers of *in vivo* testing." Since the sponsor chose the same dissolution method that was used for Norvasc® and did not test the ODT product in any media other than 0.01N HCl, it is recommended that dissolution

data be generated on a single lot of each strength ODT using three media (pH 1.2, 4.5, and 6.8) with the dissolution procedure proposed (Paddle method, 50 rpm and 500 mL of medium) to fully support the waiver for the 2.5-mg and 5-mg ODTs.

b. **Waiver from requirement of the pediatric requirement equity act:** A biowaiver was requested for pediatric studies. This waiver was granted by the Division of Cardiovascular-Renal Products.

4. Dissolution
   a. The firm based their in vitro dissolution test on the test approved for amlodipine conventional tablets. Evaluation of the currently approved procedure for amlodipine tablets (Pfizer) demonstrated that this method was acceptable for the Amlodipine orally disintegrating tablet. The paddle speed was reduced from 75 rpm to 50 rpm to provide a more sensitive method. The final method consists of:

      USP Apparatus II, Paddle Method, 50 rpm and 500 mL of 0.01M HCl. The recommend specification is Q —— in 15 minutes b(4)

   b. This dissolution method was also used to compare the 2.5-mg and 5.0-mg ODT formulations to the 10-mg amlodipine orally disintegrating tablet formulation used in the bioequivalence studies.
5. Labeling
   The labeling is comparable to the labeling for the approved NORVASC® Tablets, with minor changes to reflect the differences in the dosage forms.

Conclusion:

1. The firm has demonstrated the bioequivalence of a new 10-mg orally disintegrating tablet dosage form of amlodipine to the approved 10-mg conventional tablet, NORVASC®, manufactured by Pfizer Inc., under fasted and non-fasted conditions. The firm still needs to address the significant difference in the Tmax between the ODT and NORVASC® conventional tablets under both fasting and non-fasting conditions. The significant difference seen in Cmax and lnCmaxA between the two products under non-fasting conditions also needs to be addressed.
2. The waiver for in vivo studies demonstrating the bioequivalence of the 2.5-mg and the 5.0 mg orally disintegrating tablets compared to the 10-mg amlodipine orally disintegrating tablet is not acceptable. Additional dissolution profiles for the 2.5-mg and 5-mg ODTs need to be determined using pH 4.5 and pH 6.8 buffers and compared to the 10 mg biolot under the same conditions.
3. The absorption, distribution, metabolism and elimination portion of the label has been supported by the literature search submitted by the sponsor.
4. The sponsor's proposed dissolution method, which uses USP Apparatus 2 (Paddle) at 50 rpm, 500 mL of 0.01M HCl as the medium, is acceptable. The proposed specification is not acceptable. The specification recommended is Q —— in 15 minutes. b(4)
5. The firm has included a disintegration test in their regulatory specifications for release and stability.
6. The inspection completed by the Division of Scientific Investigations revealed severe deficiencies at the site conducting the bioequivalence studies. These deficiencies must be resolved prior to acceptance of the in vivo data.

Signatures

Reviewer: _____

Team Leader Concurrence _____

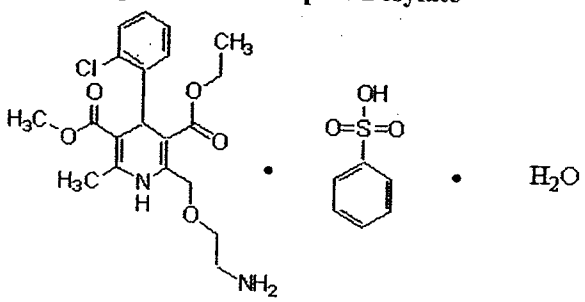
cc list: NDA 22-026; HFD-860: (Noory, Marroum, Mehta); HFD-110

2.1. GENERAL ATTRIBUTES

2.1.1. *What are the chemical and physical-chemical properties of the drug substance?*

Amlodipine is the besylate salt of amlodipine, a long-acting calcium channel blocker. Amlodipine besylate monohydrate is chemically described as 3-ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate, monobenzenesulphonate monohydrate. The molecular weight is 585.07 g/mol. Its molecular formula is C20H25ClN2O5•C6H6SO3•H2O, and its structural formula is:

Figure 1: Amlodipine Besylate



Amlodipine besylate monohydrate has one chiral center at C-4. It is marketed as a racemate. The orally disintegrating tablets are manufactured by a ——— process at Rottendorf Pharma GmbH, Ostenfelder Str. 51-61, 59320 Ennigerloh, Germany. The 2.5 mg ODT is a white, round, biconvex tablet embossed with "ADP 2.5" on one side and "ODT" on the other side. The 5 mg ODT is light yellow, round, biconvex debossed with "ADP 5" on one side and "ODT" on the other side. The 10 mg ODT is pink, round, biconvex tablet debossed with "ADP 10" on one side and "ODT" on the other side.

b(4)

2.1.2. *What is the proposed mechanism of drug action and therapeutic indication?*

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. The precise mechanisms by which amlodipine relieves angina have not been fully determined. Amlodipine relieves total ischemic burden by dilating the peripheral arterioles, thus reducing the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements. The mechanism of action of amlodipine also probably involves dilation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

2.1.3. *What is the proposed route of administration?*

Amlodipine orally disintegrating tablets are formulated to be taken orally with or without water.

2.2. CLINICAL PHARMACOLOGY

2.2.1. *What are the pharmacokinetics of amlodipine?*

The sponsor referenced the clinical pharmacology of NORVASC® tablets and the pertinent literature.

Absorption:

Orally administered amlodipine is slowly and almost completely absorbed from the gastrointestinal tract. Although the time to reach peak plasma concentration (Tmax) is 6 to 9 hours, the drug has a high bioavailability (64%-90%). Steady-state plasma concentrations in healthy volunteers are reached after 7 days.

Distribution:

The apparent volume of distribution is 21 L/kg. Similar to other calcium channel antagonists, Amlodipine is highly protein bound; protein binding is about —— *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. b(4)

Metabolism:

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism. Metabolism studies have indicated that oxidation to the pyridine analogue is the major pathway of metabolism.

Elimination:

The majority of an amlodipine dose is excreted in the urine (60%) and the feces (23%). Only small amounts (less than 5%) of the parent compound are excreted in the urine.

2.2.2. ***What are the dose and dosing regimen and are there any unresolved dosing or administration issues?***

The dose and dosing regimen are the same as labeled for NORVASC®. Amlodipine ODTs are designed to be bioequivalent to NORVASC® tablets of the same strength. There are no unresolved dosing issues. The recommended dosage of amlodipine for the treatment of hypertension and angina pectoris is 5 mg administered once daily. The dose may be increased, if necessary, to the equivalent of 10 mg of amlodipine administered once daily. A 2.5 mg dose may be used when adding amlodipine to other antihypertensive therapy. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently. The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5mg to 5mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

2.2.3. ***Are the pharmacokinetic parameters linear at steady-state?***

A three-period crossover study in which 2.5-mg, 5-mg and 10-mg amlodipine was administered showed dose proportionality with the 5-mg and 10-mg administrations. Dose proportionality was less impressive when the 2.5 mg dose was considered. The AUC, Cmax and t ½ for the 5-mg and 10-mg doses were 10-20% higher when compared to the AUC, Cmax and t ½ for the 2.5-mg dose. However, because of the small differences these will probably not be clinically relevant. Moreover, this difference may be attributed to the low plasma concentrations at the last time points which were in the region of the lower detection limit.

2.2.5. ***Was a waiver for a pediatric trial granted?***

Yes, the sponsor's request for a waiver for pediatric studies was granted by the Division of Cardio-Renal Drug Products.

2.3. INTRINSIC FACTORS

Amlodipine Orally Disintegrating Tablets are designed to be bioequivalent to NORVASC® tablets and the influence of any intrinsic factors would be expected to be the same as indicated for NORVASC® tablets and are reflected in the label.

2.4. EXTRINSIC FACTORS

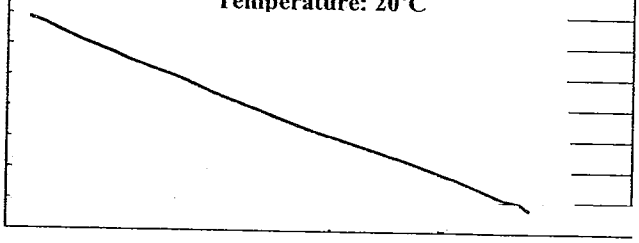
The influence of extrinsic factors and/or impact of any difference in exposure would be expected to be the same as for NORVASC® tablets. These issues are covered in the labeling in the same way as for NORVASC® tablets.

2.5. GENERAL BIOPHARMACEUTICS

2.5.1. ***What solubility, permeability, and dissolution data support this drug product's classification using BCS principles?***

To determine the BCS Classification, the solubility of the highest dose (i.e. 10 mg) must be determined in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water. Amlodipine solubility information is given in Table 1.

Table 1: Solubility of Amlodipine Besylate

SOLUBILITY	
Buffer pH	**pH of product in buffer**
Temperature: 37°C	
0.01 M HCl	3.0 mg/mL
Water	3.1 mg/mL
Temperature: 20°C	
	

b(4)

Insufficient information was submitted to determine the solubility of the product. To evaluate the solubility of the product additional solubility information across the full pH range (1-7.5) should be determined. The absolute bioavailability has been estimated to be between 64 and 90%. The dissolution information in 0.01 M HCl using the paddle apparatus at 50 rpm indicates that the product dissolves greater than — in 15minutes.

b(4)

2.5.2. ***Was bioequivalence demonstrated for the new orally disintegrating tablet dosage form when compared to the conventional tablet dosage form, NORVASC®?***

Yes, the sponsor conducted a two-period crossover, fasting bioequivalence study (Study CEPHA CPA 235-05) to determine the bioequivalence of amlodipine 10 mg orally disintegrating tablets (highest strength) dosed without water to the 10 mg NORVASC®

tablets dosed with water, when administered under fasting conditions. The 10 mg amlodipine ODT met the bioequivalence criteria when compared to NORVASC® 10 mg tablets. The 90% confidence intervals (CI) for amlodipine were (95.4-104.0%) for Cmax; (95.4-104.0%) for AUC (0-t) and (95.5-104%) for AUC (0-inf). The significant difference in Tmax between the ODT and the NORVASC® conventional tablet should be addressed. The information regarding Tmax is given in the following table:

Table 2: Information on Tmax

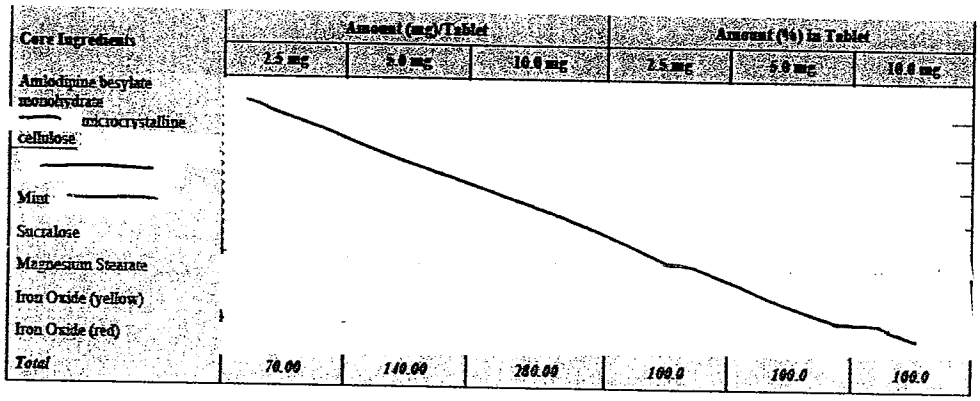
FASTING STUDY TMAX DATA			
Tmax	Test	Reference	T-R
Mean	11.09	7.17	3.92
SD	6.91	1.853	6.53
%CV	62.31	25.59	
Max	32.00	12.00	24.00
Min	6.00	4.00	-4.00
Median	9.01	7.00	-2.00

2.5.3. ***Are the 2.5 and 5.0 mg amlodipine orally disintegrating tablets bioequivalent to 10-mg ODT biolot?***

A biowaiver was requested for the lower strength based on formulation proportionality and dissolution profile similarity compared to the 10 mg strengths amlodipine ODT. The biowaiver has not been granted. The formulations are comparable and the dissolution profiles in one medium (0.01N HCl) are comparable. The firm should provide additional data for the following media: pH 4.5 and pH 6.8 using one lots of each strength compared to the 10 mg ODT biolot.

The comparability of the formulations is shown in Table 3.

Table 3: Quantitative Comparison of Formulations of Amlodipine Besylate 2.5-mg, 5-mg and 10-mg Orally Disintegrating Tablets



b(4)

Three registration batches of each strength ODT were tested using the proposed dissolution method. The dissolution profile comparability is summarized in table 4. The dissolution method used to test the ODT consisted of the paddle method, 50 rpm and 500 mL of 0.01M HCl as the medium. The Paddle method with paddles rotated at 75 rpm was used for the NORVASC® tablets.

Table 4: Dissolution Comparability of Strengths

Lot	Strength	3 min	6 min	10 min	15 min	20 min	30 min	45 min
3165901V1	2.5 mg	85	95	97	98	99	100	101
	range	72-95	85-105	87-107	89-108	90-109	93-109	95-110
3165902V2	2.5 mg	100	102	102	102	103	103	102
	Range	97-102	98-104	98-106	99-106	99-106	98-106	98-106
3165903V3	2.5 mg	77	88	93	97	100	102	103
	Range	70-85	81-94	88-97	93-101	96-103	98-105	99-107
3166001V1	5.0 mg	69	78	83	87	92	97	99
	Range	56-78	65-90	70-95	78-97	81-100	90-103	91-104
3166002V2	5.0 mg	75	81	83	87	89	94	97
	Range	64-88	69-95	72-98	74-100	77-101	81-103	88-104
3166003V3	5.0 mg	84	92	95	98	98	100	101
	Range	75-97	83-102	87-103	92-103	95-103	97-104	99-104
3166101V1	**10 mg**	**73**	**83**	**89**	**93**	**95**	**98**	**100**
	Range	**67-78**	**74-89**	**81-94**	**86-98**	**89-100**	**93-101**	**96-102**
3166102V2	10 mg	80	87	91	95	97	99	100
	Range	66-98	73-100	80-100	86-100	91-101	95-102	97-102
3166103V3	10 mg	78	84	89	92	94	97	99
	Range	72-82	78-87	81-95	84-97	87-98	91-100	96-101
4QL2W75A	10 mg	94	100	101	101	101	102	102
	Range	88-100	96-103	97-103	97-103	98-103	99-104	101-104

All batches dissolved greater than 85% in 15 minutes on average; therefore an f2 analysis is unnecessary. The 2.5-mg and the 5.0-mg tablets need to be tested in pH 4.5 buffer and pH 6.8 buffer and compared to the 10-mg amlodipine orally disintegrating tablet (biolot) as suggested in the FDA guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations".

2.5.4. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal type?

The labeling for NORVASC® states that "food does not appear to affect the systemic bioavailability". Since Amlodipine orally disintegrating 10-mg are bioequivalent to NORVASC® 100-mg tablets under fed conditions, the same statement can be included in the amlodipine orally disintegrating tablet label.

The sponsor conducted a study to determine the effect of food on the bioavailability of amlodipine orally disintegrating tablets compared to NORVASC® conventional tablets. Study CPA 236-05: A Randomized, Two-Period, Crossover, Single-dose, Bioequivalence Study on Amlodipine 10 mg ODT (Synthon Pharmaceuticals, Inc., USA) Versus NORVASC® 10 mg Tablets (Pfizer, Inc., USA) in Healthy Volunteers Under Non-Fasting Conditions, determined that the 90% confidence intervals of the relative mean for AUC0-t, AUC0-inf and Cmax was within 80% to 125%. Tmax was 9.88 hours [%CV=19.65] for amlodipine ODT and 8.08 hours [%CV=37.90] for NORVASC tablets. There was no significant difference in the kel and t ½ values between treatments (p>0.05). There were no serious adverse events reported. No significant safety concerns were raised. The results are summarized in the following table.

Table 5: Statistical Summary of Comparative Bioavailability Data

Amlodipine Tablets Dose 10 mg Ratio of Geometric Means and 90% Confidence Intervals Non-fasting Bioequivalence Study Study Number - CSP.US01.ADP.od10.002				
Parameter	**Test (Amlodipine ODT)**	**Reference (Norvasc®)**	**Ratio (%)**	**90% C.I.**
$AUC_{(0-t)}$	247.75	256.55	96.57	93.38 – 99.87
$AUC_{(0-\infty)}$	263.15	273.66	96.16	92.79 – 99.66
C_{max}	4.46	4.81	92.90	89.21 – 96.73

The sponsor should address the significant differences seen in Cmax, lnCmax and Tmax between the ODT and the reference tablet. The information is given in the following table:

Table 6: Significant Difference in Fasting Study

	TEST	REFERENCE	TEST-REFERENCE
Cmax (ng/mL)			
Mean	4.562	4.962	-0.400
SD	1.041	1.454	0.691
%CV	22.82	29.31	x
Max	7.718	10.369	0.305
Min	3.421	3.229	-2.651
Median	4.493	4.595	-0.289
lnCmax (ng/mL)			
Mean	1.496	1.5697	-0.07368
SD	0.206	0.246	0.115
%CV	13.79	15.65	x
Max	2.043	2.339	0.0896
Min	1.2299	1.1722	-0.2953
Median	1.5022	1.5249	-0.0674
Tmax (h)			
Mean	9.88	8.08	1.80
SD	1.94	3.06	2.93
%CV	19.65	37.90	
Max	12.00	12.00	8.00
Min	3.00	3.00	-2.00
Median	10.00	10.00	1.00

2.5.5. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The to-be-marketed formulation is identical to the formulation used in the pivotal clinical study.

2.5.6. Are the Sponsor's proposed dissolution medium and specifications acceptable?

No, the sponsor's proposed dissolution procedure uses the paddle method at 50 rpm with 500 mL 0.01M HCl and a tolerance specification of Q ___ in ___ minutes. The dissolution method is the same as the method approved for Norvasc® conventional tablets with the exception of the paddle speed. The paddle speed has been lowered from 75 rpm to 50 rpm to provide a more sensitive method for the ODT. The dissolution method proposed is acceptable. Based on an evaluation of the data submitted, the ODT product can meet a specification of Q ___ in 15 minutes. The final recommend dissolution procedure is b(4)

Apparatus:	Paddle Method
RPM:	50 rpm
Volume:	500 mL
Medium:	0.01N HCl
Specification:	Q ___ in 15 minutes

b(4)

2.6. ANALYTICAL

2.6.1. ***Were the correct moieties identified and properly measured?***

Yes, pharmacological testing has shown that Amlodipine is almost completely converted to inactive metabolites via hepatic metabolism. Only the parent compound was measured using a validated LC-MS/MS method.

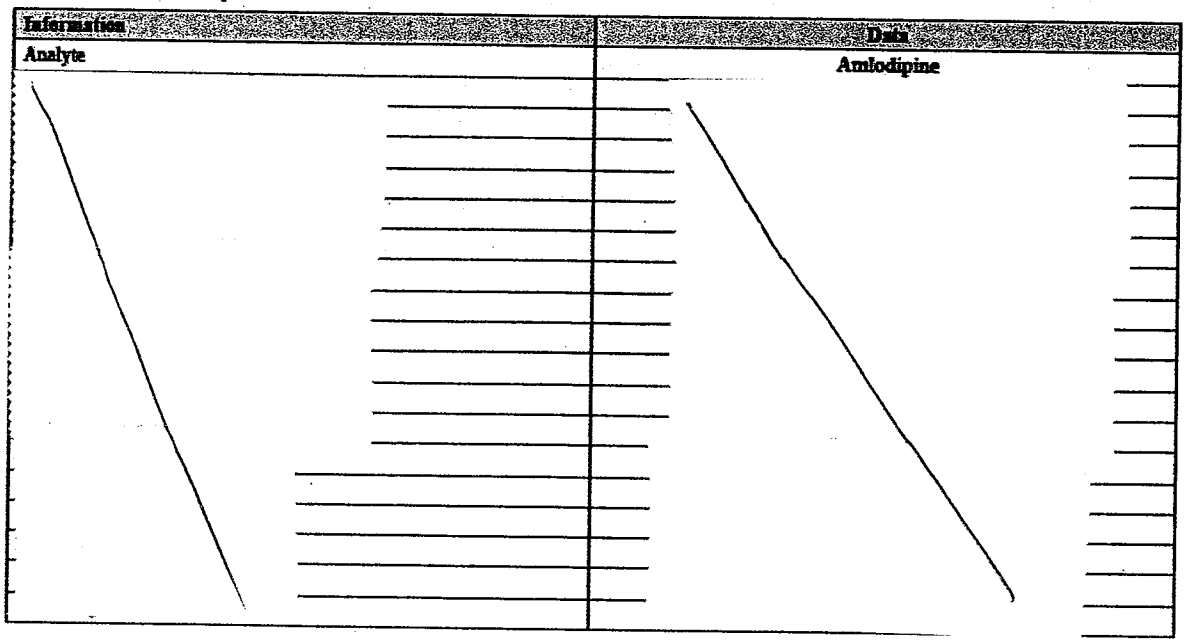
2.6.2. ***What bioanalytical methods are used to assess concentrations?***

The quantitative determination of amlodipine in plasma was performed using an HPLC/MS/MS method with ___ amlodipine as an internal standard. The lower limit of quantitation for amlodipine was 0.10 ng/mL. The bioanalytical determinations and the statistical analysis for bioequivalence were performed at ___ Amlodipine was separated from plasma using ___ procedure. Isotopically labeled (using ___ amlodipine was used as the Internal Standard (IS). ___ b(4)

b(4)

The analytical method used has been shown to be sensitive, accurate and selective for the plasma level determination of amlodipine in the concentration range of ___ No sample result exceeded this concentration range. Concentrations below the lower limit of quantitation have been considered non-quantifiable. The LC-MS/MS analytical method parameters are summarized in the following table (Table 5). b(4)

Table 7: Bioanalytical Method Validation



b(4)

The measurements were carried out at the constant mobile phase flow [redacted] Time of one analysis was 4.25 min.

b(4)

2.6.3. ***What information is available to assure that both the analytical assay and the clinical study were performed according to current GMPs and GCPs?***

An Establishment Inspection was requested for the analytical site and the clinical site.

2.6.4. ***Did the Establishment Inspection report reveal any deficiencies that may affect the outcome of the bioequivalence study submitted by the firm?***

Yes, the results of the Establishment Inspection reveal severe deficiencies at the clinical site conducting the bioequivalence studies.

3. Detailed Labeling Recommendations

Recommendation:
The Clinical Pharmacology and Dosage and Administration (Administration of Orally Disintegrating Tablets) is acceptable as proposed.

The sponsor has made the following changes to the Norvasc® label.

1. **Under CLINICAL PHARMACOLOGY: No changes**

2. **Under CLINICAL STUDIES:**

[redacted]

b(4)

3. **Under INDICATION AND USAGE.**

b(4)

4. **Under DOSAGE AND ADMINISTRATION: Added statement regarding dosing with and without water:**

Administration of ——— Orally Disintegrating Tablets: Place the orally disintegrating tablet on the tongue where it will dissolve and then be swallowed with the saliva. If necessary, follow with water. b(4)

5. **Under "HOW SUPPLIED" revised pill description, NDC number, container count to reflect our proposed brand information.**

12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio-1

4.2 INDIVIDUAL CLINICAL STUDIES

4.2.1 Bioequivalence Study: Fasting

Clinical Study CSP.US01.ADP.odt10.001
CEPHA (Clinical Facility) Study Number: CPA 235-05

b(4)

TITLE: Randomized, two-period, crossover, bioequivalence study on Amlodipine 10 mg ODT (Synthon Pharmaceuticals, Inc., USA) versus Norvasc® 10 mg Tablets (Pfizer, Inc., USA) in Healthy Volunteers under Fasting Conditions.

INVESTIGATOR: Ivan Ulč, M.D., Ph.D (CEPHA).

STUDY CENTER: CEPHA s.r.o.-Center for Pharmacology and Analysis
Komenského 19, CZ-323 00 Pilsen, Czech Republic

PHARMACOKINETIC and STATISTICAL ANALYSIS:

b(4)

STUDY PERIOD: July 9 to August 14, 2005

OBJECTIVE: This study was designed to compare the rate and extent of absorption of amlodipine 10 mg orally disintegrating tablets versus Norvasc® 10 mg tablet in healthy male and female volunteers under fasting conditions.

STUDY DESIGN: This is a two-way crossover, laboratory-blinded, single dose fasted bioequivalence study. Following an overnight fast of at least 10 hours, the subjects received 240 mL of water at 1 hour prior to the drug administration and at 1 hour after the dose. At the time of tablet administration, subjects received the ODT with no co-administered water; subjects receiving the Reference tablet received 240 mL of water concomitantly with the tablet.

Treatment:			
Product	Test/Reference	Manufacturer	Batch
Amlodipine 10 mg ODT	Test	Synthon Pharmaceutical	3166101V1 (—— tablet batch) manufactured 2-15-05 Expire 8/2005
Norvasc 10 mg Tablet	Reference	Pfizer, Inc.	4QL275A (Expires 11/2008)

b(4)

BLOOD SAMPLE COLLECTION: 8 mL of blood were collected at 0.0 (predose), 0.5 (30 minutes), 1.0*, 2.0, 3.0*, 4.0, 5.0*, 6.0, 7.0, 8.0*, 10.0, 12.0*, 16.0, 24.0*, 32.0*, 48.0*, 72.0*, 96.0*, 144.0*, and 192.0* hours post-dose. Sitting blood pressure and heart rate measurements were taken before dosing and at each * sampling time.

SAFETY ASSESSMENT: Sitting blood pressure and heart rate were measured before dosing and after the drug administration at times marked with a * above. Adverse events were monitored and a physical exam including blood chemistries, hematology and urinalysis were completed prior to dosing and following the final PK sample.

SUBJECTS:

Twenty-six normal healthy, male and female Caucasian subjects (13 males and 13 females) were enrolled in the study. Subjects were between the ages of 18 and 55 years (mean $\pm$ SD = 31.8 $\pm$ 9.4 years). Twenty-five subjects completed the study. 24 subjects were evaluated for bioequivalence assessment and 26 subjects were evaluated for safety analysis.

Table 2. Demographic Profile of Subjects Completing the Fasting Study and Included into PK Evaluation

	Fasting Bioequivalence Study Study Number: CSP.US01.ADP.odt10.001
Age (y)	
Mean ± SD	32.5 ± 9.5 years
Male	30.9 ± 7.0 years
Female	34.0 ± 11.7 years
Range	18 – 55 years
Male	23 – 45 years
Female	18 – 55 years
Groups	
<18	0 (0%)
18-39	17 (70.8%)
40-64	7 (29.2%)
65-75	0 (0%)
>75	0 (0%)
Sex	
Male	12 (50%)
Female	12 (50%)
Race	
Asian	---
Black	---
Caucasian	24 (100%)
Hispanic	---
Other	---

ANALYTICAL METHOD:

A validated HPLC-MS/MS method was employed for the analysis of amlodipine in human plasma. Plasma samples were frozen and stored at -20°C prior to analysis by [redacted] b(4)
[redacted] Amlodipine and the internal standard [isotopically labeled (using [redacted] amlodipine] were extracted by solid-phase extraction. An aliquot of this extract was injected into a HPLC system and separated by [redacted] chromatography. The mass spectrometry assay was performed using [redacted]

[redacted] b(4)

Evaluation of the assay was carried out by the construction of an eight point calibration curve covering the range of 0.10 ng/mL to 15.00 ng/mL (in human plasma) and six quality control samples (QCs) at three concentration levels distributed within one analytical batch. No instability of amlodipine in human plasma at room temperature was observed both under light and dark conditions during 24 hours. A summary of the system performance is given in the following table.

TABLE 3. ANALYTICAL METHOD PERFORMANCE			
Parameter	N=	strength	Amlodipine
Dates of analysis	8/16/2005 to 8/24/2005		
Analytical method			LC-MS/MS
Matrix			Plasma
Determination			Weighted linear regression analysis (1/conc 2)
		Standards	
Calibration curve range			0.10 ng/mL to 15.00 ng/mL
Linearity	n=25	0.10-15.00 ng/mL	0.99874
Slope			0.00534
%CV			0.19814
LLQ			0.10 ng/mL
Interday Precision %CV	N=6	0.10	5.56
	N=6	0.30	4.82
	N=6	1.00	3.79
	N=6	3.00	2.35
	N=6	6.00	2.60
	N=6	9.00	2.12
	N=6	12.00	1.76
	N=6	15.00	1.17
Interday Accuracy %RE	N=6	0.10	100.43
	N=6	0.30	100.57
	N=6	1.00	99.47
	N=6	3.00	99.92
	N=6	6.00	99.32
	N=6	9.00	99.77
	N=6	12.00	100.70
	N=6	15.00	99.89
Recovery	N=6	0.20	84.7
	N=6	3.00	94.8
	N=6	10.00	82.5
Recovery of Internal Std.	N=6		86.7
Quality Control Samples			
Interday Precision (%CV)	N=50	0.30ng/mL	6.42
	N=50	6.00 ng/mL	2.53
	N=50	12.00 ng/mL	3.09
Interday Accuracy (%RE)	N=50	0.30ng/mL	101.73
	N=50	6.00 ng/mL	102.03
	N=50	12.00 ng/mL	98.70n

PHARMACOKINETICS

Statistical Methods: Using 24 subjects, the statistical power of the study to detect a 20% difference as statistically significant in $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$ and C_{max} (ln-transformed) parameters was calculated as 99.99%. Analysis of variance was performed using SAS GLM procedures. The following pharmacokinetic parameters were calculated and statistically analyzed: AUC (0-t), $AUC_{(0\text{-}\infty)}$, Cmax, Tmax, kel, and $t_{1/2}$, ln-transformed parameters $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, C_{max} and $C_{max}/AUC_{0\text{-}\infty}$). The analysis of variance (ANOVA) was performed using the General Linear Model (GLM) procedure, in which the SEQUENCE, SUBJECT (nested in sequence), PERIOD

and TREATMENT effects were characterized. The 90% confidence interval of geometric least square means ratio T/R for AUC (0-t), $AUC_{(0-\infty)}$, and Cmax were the primary parameters for the assessment of bioequivalence.

Results:

The summary of the pharmacokinetic parameters for amlodipine geometric mean of non-transformed values are given in the following table.

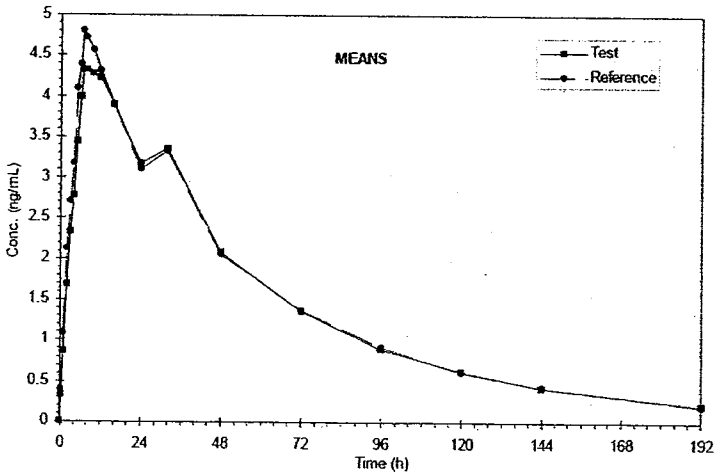
TABLE 4: Pharmacokinetic results (%CV)			
Pharmacokinetic parameter	**Amlodipine**	**Norvasc Amlodipine**	**Ratio (T/R)**
AUC (0-t) ng·hr/mL	266.01 (36.71)	269.72 (37.85)	98.62
AUC (0-inf) ng·hr/mL	283.23 (36.94)	286.57 (37.66)	98.83
Cmax (ng/mL	4.554 (32.33)	4.972 (33.03)	91.58
$Ln(Cmax/AUC_{(0-inf)})$	0.0165 (4.45)	0.0179 (5.07)	92.09
Tmax (hr)	11.09 (62.31)	7.17 (25.59)	154.67
T ½ (hr)	45.12 (25.90)	45.40 (26.78)	99.36
Kel (hr^{-1})	0.0165 (28.73)	0.0163 (25.74)	101.20
N=24			

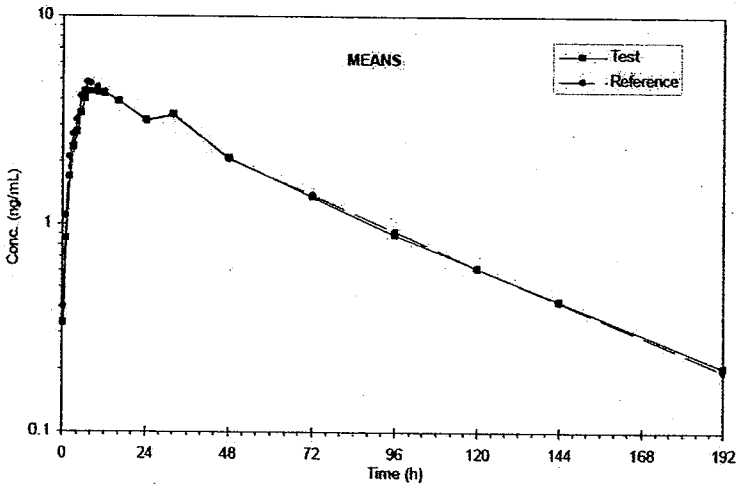
The statistical results are given in the following table.

TABLE 5: BIOEQUIVALENCE ASSESSMENT					
Parameter	**Geometric Least Square Means**		**Ratio of Means (T/R) %**	**90% CI Limits (%)**	
	Amlodipine	**Norvasc**		**Lower**	**Upper**
AUC (0-t) ng·hr/mL	246.58 (7.59)	247.50 (8.22)	99.63	95.44	104.00
AUC (0-inf) ng·hr/mL	262.08 (7.61)	263.11 (8.10)	99.61	95.47	103.93
Cmax (ng/mL	4.31 (23.83)	4.70 (22.68)	91.73	87.63	96.03

The mean ln-transformed data are shown graphically (linear and semi logarithmic scales) for amlodipine in the following figures.

Amlodipine Plasma Levels (N = 24)





SAFETY ASSESSMENT

There were no serious adverse events (AEs) reported. None of the subjects withdrew due to AEs. A total of four AEs (2 for the test and 2 for the reference) were reported by 3 subjects during the study. There were two cases of headache of the migraine type and one case of headache and one case of diarrhea. The relationship to the study drug was considered "not" responsible for any of the AEs. No significant safety concerns were raised. A summary of the AEs is shown in the following table.

Table 6: Incidence of Adverse Events

Body System/ Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. CSP.US01.ADP.odt10.001	
	Test	Reference
	Subjects (N=25)	Subjects (N=26)
Nervous System Disorders		
Headache	—	1 (3.8%)
Migraine	1 (4.0%)	1 (3.8%)
Gastrointestinal Disorders		
Diarrhoea	1 (4.0%)	—
Total Subjects with AEs within Study (%)	*2 (8.0%)	*2 (7.7%)

(*Number of subjects experiencing adverse events)

CONCLUSION

1. Based on the statistical results for Amlodipine, the 90% confidence intervals of the least square means based on ln-transformed data for AUC0-t, AUC 0-inf and Cmax of the test compared to the reference formulation was found to be within the range of 80% -125%.
2. The difference between the Cmax and the ln(Cmax/AUC0-inf) of the two treatments according to ANOVA analysis was found significant at the 5% significance level due to very high statistical power (residual variability CVres was only 9.26% for ln-transformed Cmax.). The total exposure to amlodipine was similar between the two treatments.
3. The median of Tmax was 9.02 hours (range 6.00 – 32.00) for the Test formulation and 7.00 hours (range 4.00 – 12.00) for the Reference formulation. The mean of Tmax was 11.09 hours for the Test formulation and 7.17 hours for the Reference formulation. A significant

difference was observed for Tmax between the two treatments according to Wilcoxon and median non-parametric tests and ANOVA. This difference should be addressed by the sponsor.

4. The mean of Kel was 0.0164 hours-1 for the Test formulation and 0.163 hours-1 for the Reference formulation, while mean t ½ value was 45.12 and 45.40 hours following the same order. The coefficient of variation of kel was approximately 29% and 26% for the Test and Reference formulations, respectively. Difference between the two treatments for Kel and t ½ according to ANOVA analysis and Wilcoxon and median non-parametric tests was not significant at 5% level.

Safety:

There were no serious adverse events reported and no significant safety concerns were raised.

4.2.2. Bioequivalence Study: Non-Fasting

Clinical Study CPA 236-05
(CSP.US01.ADP.odt10.002)

b(4)

TITLE: Randomized, two-period, crossover, bioequivalence study on Amlodipine 10 mg ODT (Synthon Pharmaceuticals, Inc., USA) versus Norvasc® 10 mg Tablets (Pfizer, Inc., USA) in Healthy Volunteers under Non-Fasting Conditions.

INVESTIGATOR:
STUDY CENTER:

b(4)

PHARMACOKINETIC and STATISTICAL ANALYSIS:

b(4)

STUDY PERIOD: July 23, 2005 to August 30, 2005

OBJECTIVE: This study was designed to compare the rate and extent of absorption of amlodipine 10 mg orally disintegrating tablets versus Norvasc® 10 mg tablet in healthy male and female volunteers under non-fasting conditions.

STUDY DESIGN: This is a two-way crossover, laboratory-blinded, single dose fed bioequivalence study. Subjects received 240 mL of water 1 hour prior to dose administration. Standardized meals were provided 11 hours and 0.5 hours prior to dosing. The TEST formulation (ODT) was administered without water. The REFERENCE formulation was administered with 240 mL of water.

Treatments:			
Product	Test/ Reference	Manufacturer	Batch
Amlodipine 10 mg ODT	Test	Synthon Pharmaceutical	3166101V1 (—— tablet batch) manufactured 2-15-05 Expire 8/2005
Norvasc 10 mg Tablet	Reference	Pfizer, Inc.	4QL275A (Expires 11/2008)

b(4)

STANDARDIZED MEAL (BREAKFAST): The following standardized breakfast was provided 30 minutes prior to dose administration.

STANDARDIZED MEAL (BREAKFAST) COMPOSITION				
Composition	**Energy (kJ)**	**Protein (g)**	**Fat (g)**	**Sugar (g)**
2 slices of toast with butter (10 g); 2 eggs fried in butter; 2 strips of bacon (40 g); hash brown potatoes (120g); whole milk (240 mL)	3563 (851 calories)	26.1	55.1	62.6

BLOOD SAMPLE COLLECTION: 8 mL of blood were collected at 0.0 (predose)*, 0.5 (30 minutes), 1.0, 2.0, 3.0*, 4.0, 5.0*, 6.0, 7.0, 8.0*, 10.0, 12.0*, 16.0, 24.0*, 32.0*, 48.0*, 72.0*, 96.0*, 120.0*, 144.0*, and 192.0* hours post-dose.

SAFETY ASSESSMENT: Sitting blood pressure and heart rate were measured before dosing and after the drug administration at times marked with a * above. Adverse events were monitored and a physical exam including blood chemistries, hematology and urinalysis were completed prior to dosing and following the final PK sample.

SUBJECTS:
Twenty-six normal healthy, male and female Caucasian subjects (13 males and 13 females) were enrolled in the study. Subjects were between the ages of 19 and 46 years (median = 28.0 years) and 159.0 to 189.5 cm tall (median 175.0 cm). Their weight was between 57.7 kg and 91.5 kg (median 69.05 kg). Their BMI was between 20.0 and 26.9 (median 23.1). Nineteen of the subjects were non-smokers, seven volunteers smoked up to 10 cigarettes per day. All twenty-six subjects completed the study.

Table 2. Demographic Profile of Subjects Completing the Non-fasting Study and Included into PK Evaluation

	Non-fasting Bioequivalence Study Study Number: CSP.US01.ADP.od(10.002
Age (y)	
Mean ± SD	29.0 ± 7.8 years
Male	26.5 ± 6.3 years
Female	31.6 ± 8.6 years
Range	19 – 46 years
Male	19 – 41 years
Female	31 – 46 years
Groups	
<18	0 (0%)
18-39	20 (83.3%)
40-64	4 (16.7%)
65-75	0 (0%)
>75	0 (0%)
Sex	
Male	12 (50%)
Female	12 (50%)
Race	
Asian	---
Black	---
Caucasian	24 (100%)
Hispanic	---
Other	---

ANALYTICAL METHOD:
A validated HPLC-MS/MS method was employed for the analysis of amlodipine in human plasma. Plasma samples were frozen and stored at -20°C prior to analysis by [redacted] Amlodipine and the internal standard [isotopically labeled (using [redacted]

b(4)

amlodipine] were extracted by solid-phase extraction. An aliquot of this extract was injected into a HPLC system and detected using a tandem mass spectrometer. The analytes were separated by [redacted] chromatography. The mass spectrometry assay was performed using [redacted]

b(4)

Evaluation of the assay was carried out by the construction of an eight point calibration curve covering the range of 0.10 ng/mL to 15.00 ng/mL (in human plasma) and six quality control samples (QCs) at three concentration levels distributed within one analytical batch. A summary of the system performance is given in the following table.

TABLE 3: BIOANALYTICAL METHOD VALIDATION

Parameter	N=	strength	Amlodipine
Dates of analysis	9-5-2005 to 9-13-2005		
Analytical method			LC-MS/MS
Matrix			Plasma
Determination			Weighted linear regression analysis (1/conc 2)
		Standards	
Calibration curve range			0.10 ng/mL to 15.00 ng/mL
Linearity	n=25	0.10-15.00 ng/mL	0.99874
Slope			0.00534
%CV			0.19814
LLQ			0.10 ng/mL
Interday Precision %CV	N=6	0.10	3.92
	N=6	0.30	2.87
	N=6	1.00	2.74
	N=6	3.00	1.98
	N=6	6.00	1.68
	N=6	9.00	1.40
	N=6	12.00	1.61
	N=6	15.00	1.41
Interday Accuracy %RE	N=6	0.10	102.89
	N=6	0.30	99.55
	N=6	1.00	98.43
	N=6	3.00	98.53
	N=6	6.00	99.98
	N=6	9.00	99.90
	N=6	12.00	101.29
	N=6	15.00	99.42
Recovery	N=6	0.20	84.7
	N=6	3.00	94.8
	N=6	10.00	82.5
Recovery of Internal Std.	N=6	5.00	86.7
	N=6	3.00	
	N=6	10.00	
Quality Control Samples			
Interday Precision (%CV)	N=50	0.30ng/mL	3.80
	N=50	6.00 ng/mL	2.70
	N=50	12.00 ng/mL	2.88

TABLE 3: BIOANALYTICAL METHOD VALIDATION			
Parameter	N=	strength	Amlodipine
Interday Accuracy (%RE)	N=50	0.30ng/mL	103.17
	N=50	6.00 ng/mL	102.06
	N=50	12.00 ng/mL	103.02

PHARMACOKINETICS

Statistical Methods: Using 24 subjects, the statistical power of the study to detect a 20% difference as statistically significant in $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} (ln-transformed parameters) was calculated as 99.99%. The following pharmacokinetic parameters were calculated and statistically analyzed: AUC (0-t), $AUC_{(0-\infty)}$, Cmax, Tmax, kel, and $t_{1/2}$, ln-transformed parameters $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max} and $C_{max}/AUC_{0-\infty}$). The analysis of variance (ANOVA) was performed using the General Linear Model (GLM) procedure, in which the SEQUENCE, SUBJECT (nested in sequence), PERIOD and TREATMENT effects were characterized. The 90% confidence interval of geometric least square means ratio T/R for AUC (0-t), $AUC_{(0-\infty)}$, and Cmax were the primary parameters for the assessment of bioequivalence.

Results:

The summary of the pharmacokinetic parameters for amlodipine geometric mean of non-transformed values are given in the following table.

Table 4: Summary of ADP pharmacokinetic parameters

Parameter	TEST		REFERENCE		RATIO T/R (%)	F (Treatment)	Pr > F (Treatment)
	MEAN	CV (%)	MEAN	CV (%)			
$AUC_{(0-t)}$ (ng·h/mL)	254.77	24.25	262.58	22.74	97.03	2.10	N.S.
$ln(AUC_{(0-t)})$ (ng·h/mL)	247.75*	4.39	256.55*	3.92	96.57	3.18	N.S.
$AUC_{(0-inf)}$ (ng·h/mL)	270.53	23.96	280.48	23.18	96.45	2.62	N.S.
$ln(AUC_{(0-inf)})$ (ng·h/mL)	263.15*	4.33	273.66*	4.00	96.16	3.54	N.S.
C_{max} (ng/mL)	4.562	22.82	4.962	29.31	91.94	7.76	S.
$ln(C_{max})$ (ng/mL)	4.464*	13.79	4.805*	15.65	92.90	9.77	S.
$ln(C_{max}/AUC_{(0-inf)})$ (h^{-1})	0.0170*	4.62	0.0176*	4.63	96.61	1.89	N.S.
t_{max} (h)	9.88	19.65	8.08	37.90	122.22	9.42	S.
k_{el} (h^{-1})	0.0164	22.35	0.0155	26.48	105.72	1.51	N.S.
$t_{1/2e}$ (h)	44.54	24.27	48.60	33.21	91.64	1.98	N.S.

* geometric mean of non-transformed parameter, i.e. exp(MEAN of ln(PK)), where PK are values of relevant pharmacokinetic parameter.

Note: S. = significant, N.S. = non-significant at the 5% significance level

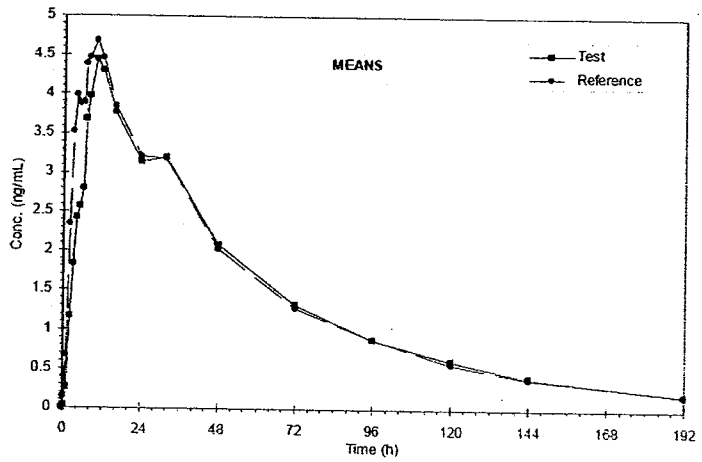
The statistical results are given in the following table.

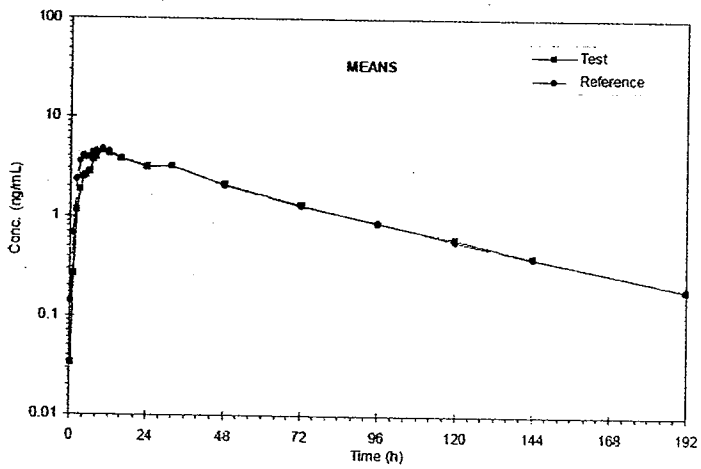
Table 5: Statistical Summary of Comparative Bioavailability Data

Amlodipine Tablets Dose 10 mg Ratio of Geometric Means and 90% Confidence Intervals Non-fasting Bioequivalence Study Study Number: CSP.US01.ADP.odt10.002				
Parameter	**Test (Amlodipine ODT)**	**Reference (Norvasc®)**	**Ratio (%)**	**90% C.I.**
$AUC_{(0-t)}$	247.75	256.55	96.57	93.38 – 99.87
$AUC_{(0-\infty)}$	263.15	273.66	96.16	92.79 – 99.66
C_{max}	4.46	4.81	92.90	89.21 – 96.73

The mean ln-transformed data are shown graphically (linear and semi logarithmic scales) for amlodipine in the following figures.

Amlodipine Plasma Levels (N=24)





SAFETY ASSESSMENT

There were no serious adverse events reported. There were eighteen adverse events; ten cases of headache, three cases of nausea, two cases of drowsiness (somnolence), and single cases of fatigue, diarrhea and low back pain occurred in 10 subjects. Severity of AEs was mild (5 cases) or moderate (13 cases). The relationship of the adverse events to the study medication was judged as "possibly related" in 17 cases. No significant safety concerns were raised.

Table 6: Incidence of Adverse Events

Body System/ Adverse Event	Reported Incidence by Treatment Groups Non-Fasting Bioequivalence Study Study No. CSP.US01.ADP.od410.002	
	Test Subjects (N=26)	Reference Subjects (N=26)
General Disorders and Administrative Site Conditions		
Fatigue	—	1 (3.8%)
Nervous System Disorders		
Headache	6 (23.1%)	4 (15.4%)
Somnolence	1 (3.8%)	1 (3.8%)
Gastrointestinal Disorders		
Diarrhea	—	1 (3.8%)
Nausea	1 (3.8%)	2 (7.7%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	1 (3.8%)	—
Total Subjects with AEs Within Study (%)	*8 (30.8%)	*7 (26.9%)

(*Number of subjects experiencing adverse events)

CONCLUSION

- Based on the statistical results for Amlodipine, the 90% confidence intervals based on ln-transformed data for AUC0-t, AUC 0-inf and Cmax of the test compared to the reference formulation was found to be within the range of 80% -125%.
- A significant difference at the 5% significance was found between the Cmax and the ln(Cmax) of the two treatments according to ANOVA analysis. This should be addressed by the sponsor.
- The mean of Tmax was 9.88 hours for the Test formulation and 8.08 hours for the Reference formulation. A significant difference was observed for Tmax between the two treatments according to Wilcoxon and median non-parametric tests and ANOVA. This should be addressed by the sponsor.
- The mean of Kel was 0.0164 hours-1 for the Test formulation and 0.155 hours-1 for the Reference formulation, while mean t ½ value was 44.54 and 48.60 hours following the same order. The coefficient of variation of Kel was approximately 22% and 26% for the Test and Reference formulations, respectively. Difference between the two treatments for Kel and t ½ according to ANOVA analysis and Wilcoxon and median non-parametric tests was not significant at 5% level.

Safety:

There were no serious adverse events reported and no significant safety concerns were raised.

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 2

APPENDIX 4.3 DISSOLUTION PROCEDURE EVALUATION

The firm submitted dissolution data on three lots of each strength of ODT for which they are seeking approval. The dissolution test used the medium and apparatus approved for Norvasc®. The paddle speed was lowered from 75 rpm to 50 rpm to provide for a more sensitive method. The final method is:

Apparatus:	Paddle Method
RPM:	50 rpm
Medium:	0.01M HCl
Volume:	500 mL

The firm is requesting a specification of Q —— in — minutes. The following data was submitted (Table 1) b(4)

Table 1: Summary of in vitro dissolution Studies (n=12)

Dissolution Lot	Method Strength	P 50 rpm; 500 mL of 0.01 M HCl 3	6	10	15	20	30	45
3165901V1	**2.5**	85.1	95.1	96.6	98.1	98.8	100.0	101.3
		72.1-94.7	85.2-105.0	87.0-106.9	88.6-108.3	90.4-108.7	92.9-109.2	95.1-109.6
3165902V2	2.5	100.0	102.0	102.0	102.0	103.0	103.0	102.0
		97-102	98.0-104.0	98.0-106.0	99.0-106.0	99.0-106.0	98.0-106.0	98.0-106.0
3165903V3	2.5	77.0	88.0	93.0	97.0	100.0	102.0	103.0
		70.0-88.0	81.0-94.0	88.0-97.0	93.0-101.0	96.0-103.0	98.0-105.0	99.0-107.0
3166001V1	**5.0**	68.7	78.1	83.2	87.0	91.6	96.7	99.0
		56.0-78.2	65.4-90.5	70.4-95.2	77.7-97.0	81.3-99.5	89.9-103.2	91.0-104.0
3166002V2	5.0	75.0	81.0	83.0	87.0	89.0	94.0	97.0
		64.0-88.0	69.0-95.0	72.0-98.0	74.0-100.0	77.0-101.0	81.0-103.0	88.0-104.0
3166003V3	5.0	84.0	92.0	95.0	98.0	98.0	100.0	101.0
		75.0-97.0	83.0-102.0	87.0-103.0	92.0-103.0	95.0-103.0	97.0-104.0	99.0-104.0
3166101V1	**10.0**	72.7	83.1	88.8	92.9	95.5	98.3	99.6
		66.7-77.9	74.4-88.9	81.1-94.3	86.0-98.0	89.1-99.6	93.3-100.7	96.2-102.3
3166102V2	10.0	80.0	87.0	91.0	95.0	97.0	99.0	100.0
		66.0-98.0	73.0-100.0	80.0-100.0	86.0-100.0	91.0-101.0	95.0-102.0	97.0-102.0
3166103V3	10.0	78.0	84.0	89.0	92.0	94.0	97.0	99.0
		72.0-82.0	78.0-87.0	81.0-95.0	84.0-97.0	87.0-98.0	91.0-100.0	96.0-101.0
Dissolution 4QL275A	Method 10.0	P 75 rpm; 500 mL of 0.01 M HCl 93.9	99.7	100.7	101.0 97.0-	101.3	101.7	102.2
		87.7-99.8	95.7-103.0	96.6-103.5	103.5	97.8-103.5	99.0-103.9	100.6-103.9

The dissolution method is acceptable. The specification recommended is Q——; in 15 minutes based on the data evaluated. b(4)

APPENDIX 4.4 FILING REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**22-026**	**Brand Name**	
OCPB Division (I, II, III, IV, V)		**Generic Name**	**Amlodipine besylate ODT**
Medical Division	**Cardio-Renal**	**Drug Class**	**Anti hypertensive**
OCPB Reviewer	**Carol Noory**	**Indication(s)**	**Treatment of hypertension**
OCPB Team Leader	**Patrick Marroum**	**Dosage Form**	**ODTablet 2.5, 5 and 10 mg**
		Dosing Regimen	**5 – 10 mg/day**
Date of Submission	**1/31/2006**	**Route of Administration**	**oral**
Estimated Due Date of OCPB Review		**Sponsor**	**Synthon Pharmaceutical**
PDUFA Due Date		**Priority Classification**	**S**
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				

solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	68			
Total Number of Studies	[redacted]			

Filability and QBR comments

	"X" if yes	Comments
Application fileable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1. Acceptable BE** **2. Acceptable FE study** **3. Approval of Biowaiver** **4. Proportional Formulation** **5. Linear Pharmacokinetics** **6. Acceptable Dissolution Method** **7. Adequate Dissolution Specification** **8. Acceptability of Pediatric Waiver Request**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carol Noory
11/1/2006 02:39:07 PM
BIOPHARMACEUTICS

Patrick Marroum
11/13/2006 04:34:55 PM
BIOPHARMACEUTICS

New Drug Application –Response to Information Request
Clinical Pharmacology and Biopharmaceutics Review

NDA:	22-026 (000 BZ)
Type of Submission:	Response to information requested in Approvable Letter
Generic Name:	Amlodipine Besylates
Formulation:	Orally Disintegrating Tablets
Strengths:	2.5mg, 5 mg, and 10 mg
Route:	Oral
Brand Names	Not given
Sponsor:	Synthon Pharmaceuticals, Inc. Research Triangle, North Carolina
Submission Dates:	March 27, 2007
Reviewer:	Carol Noory

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II. EXECUTIVE SUMMARY

A. Recommendation

The Office of Clinical Pharmacology / Division of Pharmaceutical Evaluation I (OCP/DPE-1) has reviewed the response to the information requested for NDA 22-026 submitted March 27, 2007. OCP finds the Clinical Pharmacology and Biopharmaceutics portion of NDA 22-026 acceptable provided the changes outlined in the Comments Section (see § *Comments to the Sponsor* on page13) are adequately addressed. The biowaiver requested for the 2.5 mg and 5.0 mg ODTs is acceptable. Comparison of the original fasting study and the repeat fasting study should be sufficient to address the deficiencies cited in the DSI audit.

B. Introduction / Background

1. Clinical Pharmacology

Amlodipine is used clinically for the treatment of hypertension; for the symptomatic treatment of chronic stable angina; and for the treatment of confirmed or suspected vasospastic angina.

2. Regulatory History of Amlodipine

Amlodipine is currently approved in the US for oral administration. Synthon Pharmaceuticals Inc. has developed a new orally disintegrating tablet that provides a pharmaceutical alternative to NORVASC® immediate-release conventional tablets manufactured by Pfizer. The original NDA for amlodipine orally disintegrating tablets received an approvable letter from the Division of Cardio-Renal Drug Products on December 1, 2006. There were several question regarding this application and additional questions regarding the conduct of clinical trial sponsored by Synthon ——————————— b(4)
Amlodipine besylate tablets (ANDA 77-080) and Simvastatin orally disintegrating tablets (NDA 21-961). These applications are being held pending the outcome of the bioavailability study submitted with this NDA (NDA 22-026).

3. Current Submission

The current submission is in response to questions raised by the agency regarding NDA 22-026 as well as the conduct of several clinical studies sponsored by Synthon Pharmaceuticals, Inc. for other applications pending within the agency.

The sponsor has provided additional information needed to address the following issues for NDA 22-026:

- Differences in Tmax values between the TEST and REFERENCE treatments in the original fasting BA study
- Support for the approval of the waiver for biostudies for the lower strengths, 2.5 mg and 5 mg ODT by providing adequate dissolution data
- Justification of the dissolution method and selection of media
- Justification of the dissolution specification

For NDA 22-026 and certain other applications pending within the agency, the sponsor has provided information to address the following issue:

- Deficiencies noted by the Division of Scientific Investigation regarding the conduct of clinical studies sponsored by Synthon Pharmaceuticals by conducting and submitting a repeat fasting BA study and comparing the results to the original fasting BA study

III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

A. Differences in Tmax values between the TEST and REFERENCE Treatments

In the original submission, a significant difference was observed for Tmax between the TEST and the REFERENCE treatments in the fasting bioavailability study according to Wilcoxon, median non-parametric tests and ANOVA. The mean of Tmax was 11.09 hours (6 hours – 32 hours) for the TEST formulation and 7.17 hours (4 hours – 12 hours) for the REFERENCE formulation (
Table 1: Amlodipine: ANOVA for Tmax for 24 Subjects for original study).

Table 1: Amlodipine: ANOVA for Tmax for 24 Subjects for original study

Source of variation	DF	Sum of Squares	Mean Squares	F	Pr>F
Seq	1	24.01255208	24.01255208	0.80	0.3807
Subject (Seq)	22	660.0404858	30.0018403	1.38	0.2262
Period	1	14.0292187	14.0292187	0.65	0.4298
Treatment	1	184.27921880	184.27921880	8.50	0.0080
Residual	22	496.99239	21.681472	-	-
Intra-subject CV = 51.01%					
Inter-subject CV = 22.35%					
GrandMean = 9.13					
Median (one way) test for treatment Chi-Square 4.4834 Pr > Chi-Square 0.0342					
Wilcoxon (Kruskal- Wallis) test for treatment Chi-Square 8.6716 Pr > Chi-Square 0.0032					

Synthon was requested to submit information to address the significant difference in Tmax between the Test and Reference products seen in the original fasting bioavailability study. In response to this request, the firm evaluated the early exposure of the drug by calculating the partial AUC 0-7 hours. This procedure is recommended by the CDER guidance, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations*. The partial AUC was truncated at the population medial of Tmax for the REFERENCE treatment. The AUC was calculated using a

total of 9 time points (0, 0.5, 1, 2, 3, 4, 5, 6, and 7 hours) and the data is presented in the following table (Table 2).

Table 2: Early Exposure Data

Parameter	Geometric Least Squares Mean		Ratio T/R	90% Confidence Interval	
	Test	Reference		Lower	Upper
AUC0-7h	19.897	17.192	0.864	81.18	91.63

The repeated fasting bioavailability study results for Tmax did not show a significant difference in Tmax between the two treatments (Table 3).

Table 3: Amlodipine: ANOVA for Tmax for 24 Subjects for repeat study

Source of variation	DF	Sum of Squares	Mean Squares	F	Pr>F
Seq	1	0.32785602	0.32785602	0.05	0.8306
Subject (Seq)	22	153.935159	6.9970527	2.46	0.0200
Period	1	5.2887602	5.2887602	1.86	0.1864
Treatment	1	0.09178750	0.09178750	0.03	0.8591
Residual	22	62.5575858	2.8435266	-	-
Intra-subject CV = 20.54%					
Inter-subject CV = 17.55%					
GrandMean = 8.21					
Median (one way) test for treatment Chi-Square 0.0145 Pr > Chi-Square 0.9041					
Wilcoxon (Kruskal- Wallis) test for treatment Chi-Square 0.0071 Pr > Chi-Square 0.9326					

B. **Waiver for biostudies for the lower strength, 2.5 mg and 5 mg ODT.**

The waiver requested for the lower strengths, 2.5-mg and 5.0-mg strength orally disintegrating tablets (ODTs), was not granted in the original submission. The firm was requested to submit additional dissolution data to support the biowaiver requested. Dissolution data was submitted using the proposed method (paddle method, 50 rpm) comparing the lower 2.5 mg and 5 mg strength ODT to the

10 mg strength ODT used in the in vivo studies. Profiles were generated in 500 mL of the following three media:

- pH 1.2: 0.01M Hydrochloric Acid
- pH 4.5 Phosphate Buffer
- pH 6.8 Phosphate Buffer

Results of the dissolution (Table 4) indicate that the dissolution is rapid and complete in all media, with the dissolution rate being slightly slower in pH 6.8 phosphate buffer (Figure 1: Dissolution in 0.01M HCl, Figure 2: Dissolution in pH 4.5 Phosphate Buffer, Figure 3: Dissolution in pH 6.8 Phosphate Buffer). The f2 profile similarity factor was only appropriate for the pH 6.8 phosphate buffer.

Table 4: Dissolution Comparison

DISSOLUTION COMPARISON OF 2.5 MG, 5.0 MG AND 10 MG AMLODIPINE ODT IN THREE MEDIA USING THE PADDLE METHOD 50 RPM								
paddle method; 50 rpm; 500 ml of media								
	Medium	**0.01 M HCL**						
Strength	**Time**	**0**	**3**	**6**	**10**	**15**	**20**	**30**
2.5 mg	Mean	0	85	95	97	98	99	100
	Range	0	72-95	85-105	87-107	89-108	90-109	93-109
5.0 mg	Mean	0	69	78	83	87	92	97
	Range	0-0	56-78	65-90	70-95	78-97	81-100	90-103
10.0 mg	Mean	0	73	83	89	93	95	98
	Range	0-0	67-78	74-89	81-94	86-98	89-100	93-101
	Medium	**pH 4.5 Phosphate buffer**						
Strength	**Time**	**0**	**3**	**6**	**10**	**15**	**20**	**30**
2.5 mg	Mean	0	87	93	97	98	102	102
	Range	0-0	70-107	82-122	90-113	92-103	95-127	96-107
5.0 mg	Mean	0	73	80	83	87	90	95
	Range	0-0	62-106	74-90	78-94	81-97	84-100	90-104
10.0 mg	Mean	0	69	78	83	89	93	97
	Range	0-0	64-81	74-89	78-91	84-96	90-98	92-100
	Medium	**pH 6.8 Phosphate Buffer**						
Strength	**Time**	**0**	**3**	**6**	**10**	**15**	**20**	**30**
2.5 mg	**Mean**	0	64	75	78	81	82	85
	Range	0-0	52-71	59-77	64-80	69-85	73-88	78-94
5.0 mg	**Mean**	0	55	63	67	70	72	76
	Range	0-0	49-64	56-76	59-82	61-87	64-90	67-93
10.0 mg	**Mean**	0	61	66	69	71	72	76
	Range	0-0	51-68	58-76	61-79	64-79	67-82	72-82
F2 in pH 6.8 phosphate buffer		2.5 mg	**52.9**					
		5.0 mg	**75.7**					

Figure 1: Dissolution in 0.01M HCl

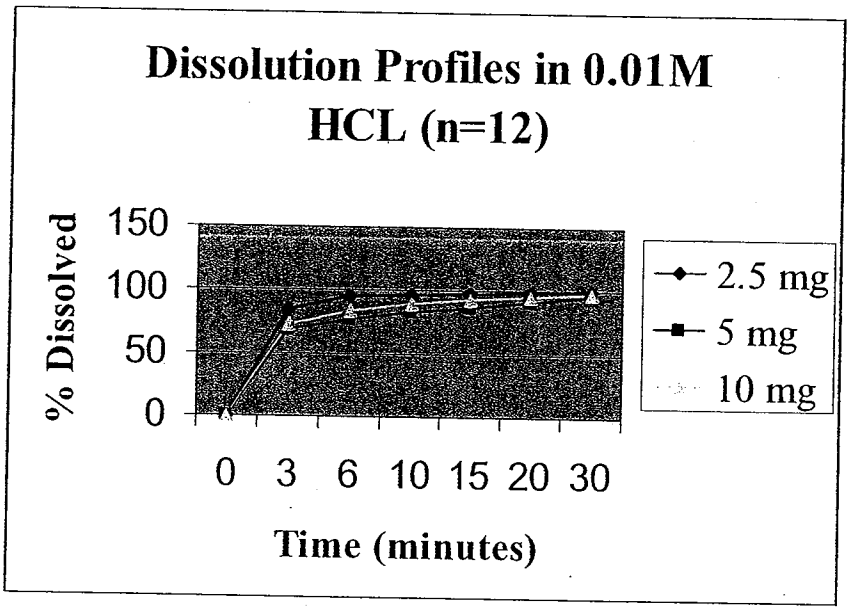


Figure 2: Dissolution in pH 4.5 Phosphate Buffer

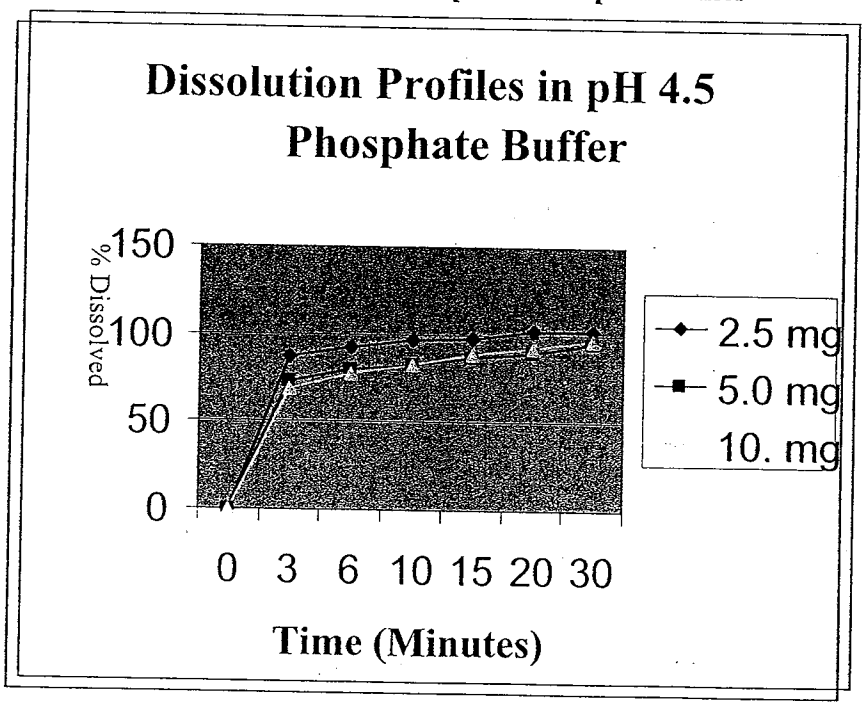
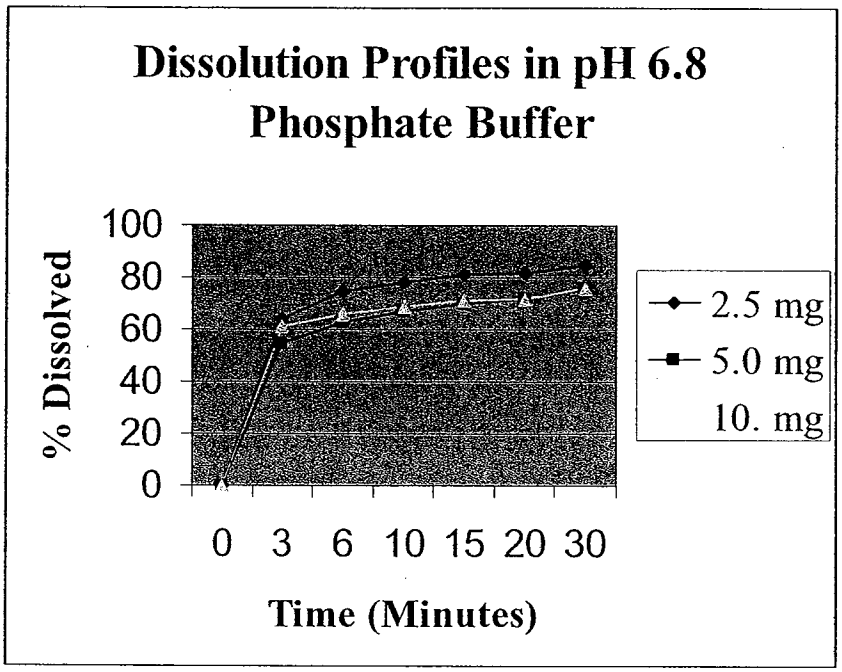


Figure 3: Dissolution in pH 6.8 Phosphate Buffer



C. Evaluation of the Dissolution Method and Selection of Media

0.01 M HCL was selected by the firm as the medium of choice. This appears to be an appropriate selection based on the dissolution data presented.

D. Evaluation of the Dissolution Specification

After evaluation of the dissolution data submitted in the original application, OCP recommended that the dissolution specification should be tightened. The following dissolution method and specification were recommended:

USP Apparatus 2: Paddle Method
Rotation speed: 50 rpm
Volume: 500 mL
Medium: 0.01 M HCl
Tolerance: Q —— in 15 minutes

b(4)

The firm has requested that the specification be Q= —— in —minutes based on dissolution data from the 9, 12 and 18 month primary stability studies. The firm submitted dissolution data for the 2.5 mg, 5.0 mg and 1.0 mg ODTs at 15 and 30 minutes.

b(4)

Table 5: Minimum dissolution values for Amlodipine besylate 2.5 mg, 5 mg and 10 mg Orally Disintegration Tablets Stability Studies at 15 minutes and 30 minutes.

Strength		15 min	30 min	15 min	30 min	15 min	30 min
2.5mg	3165901V1, 14 count	88	94	87	94	88	93
2.5mg	3165902V2, 14 count	97	98	93	97	92	101
2.5mg	3165903V3, 14 count	97	99	89	97	97	101
2.5mg	3165901V1, 30 count	91	96	92	95	89	96
2.5mg	3165902V2, 30 count	89	93	74	85	94	99
2.5mg	3165903V3, 30 count	95	100	95	100	89	96
5mg	3166001V1, 14 count	88	93	80	89	103	98
5mg	3166002V2, 14 count	75	83	87	94	104	99
5mg	3166003V3, 14 count	94	98	85	93	97	88
5mg	3166001VI, 30 count	83	87	85	94	100	97
5mg	3166002V2, 30 count	89	95	86	98	104	98
5mg	3166003V3, 30 count	89	95	87	97	99	101
10mg	3166101 VI, 14 count	97	99	88	96	98	103
10mg	3166102V2, 14 count	97	101	88	96	98	103
10mg	3166103V3, 14 count	95	98	91	98	100	97
10mg	3166101VI, 30 count	92	98	84	96	97	100
10mg	3166102V2, 30 count	102	102	89	97	100	103
10mg	3166103V3, 30 count	95	98	89	95	100	99

E. Evaluation of the repeat fasting BA study and comparison of the results

The FDA inspections revealed significant deficiencies in the documentation and procedural aspects of this bioequivalence studies conducted at CEPHA, Center for Pharmacology and Analysis. The primary concern was a lack of documentation verifying at the time of dosing and the treatment received by each subject. To resolve this issue, the sponsor was requested to repeat the fasting bioequivalence study to demonstrate that, with proper documentation and procedures, the results of an earlier study can be reproduced.

The repeat amlodipine study [comparing Synthon's 10 mg amlodipine orally disintegrating tablets (ODT) to Pfizer's NORVASC®10 mg tablets] conducted at CEPHA should address the following items:

- **Address FDA's Audit Findings:** Have adequate documentation of the drug products to assure that subjects received the intended product on each occasion. These documents should address FDA's audit findings and include records for shipment, receipt, storage, dispensing, and administration of drugs, and blood collection This criteria is being evaluated by the Division of Scientific Investigations

- **Mimic the Original Study:** The protocol should be the same for the conduct of the study and analysis of the samples. The study was conducted using the same protocol as

the original fasting study. The same lots or test and reference products were used in the study (Table 6).

Table 6: Comparison of the Test and Reference Products

(TREATMENTS: ORIGINAL AND REPEAT STUDY		
	Original Study: CPA-235-05	Repeat Study: CPA-295-06
Products		
Test Product	Lot 3166101V1	Lot 3166101V1
Reference Product	4QL275A	4QL275A

The number and gender distribution of subjects were similar to that of the original study (i.e., 13 males and 13 females) with similar age distribution (18-55 years) (Table 10: Table 10).

Table 7: Subject Demographics of the Original and Repeat Studies

SUBJECT DEMOGRAPHICS		
	Original Study: CPA-235-05	Repeat Study: CPA-295-06
Subjects		
Gender		
Male	13	13
Female	13	11
Age	18-55 (32.5 ± 9.54) year	19-50 (32.0 ± 10.1) years
Male	30.9 ± 7years	27.7 ± 7.4
Female	34.0 ± 11.7 years	36.4 ± 10.8
Groups		
<18 years	0	
19-39 years	17 (70.8%)	16 (66.7%)
40-64 years	7 (29.2%)	8 (33.3%)
Race		
Asian	0	0
Black	0	0
Caucasian	24 100%)	24 (100%)
Hispanic	0	0
Other	0	0
Height		
Mean	175.02 ± 10.42 cm	173.2 ± 8.97 cm
Range	158.5 - 195.0 cm	159.5 -189.0 cm
Weight		
Mean	71.7 ± 11.28 kg	70.3 ± 8.1 kg
Range	56.9 - 99.1 kg	58.6 – 88.3 kg
BMI		
Mean	23.30 ± 2.02	23.4 ± 2.2
Range	20.1 – 26.5	19.1 – 26.8

- **Treatment of Repeats should be the Same:** Repeats were treated in the same manner (Table 8).

Table 8: Repeats

REPEATS		
	Original Study: CPA-235-05	**Repeat Study: CPA-295-06**
Repeats	**3 test/ 2 reference (1 test and 1 reference recalculated after retest)**	**None**

- **Meet similar bioequivalence criteria (i.e., 90% confidence intervals for AUC_{0-t}, AUC_{0-inf} and Cmax within 80-125%) as the original study:** The results of the study meet the confidence intervals for AUC 0-t, AUC 0-inf, and Cmax (Table 9).

Table 9: Bioequivalence Criteria

BIOEQUIVALENCE CRITERIA				
	Original Study: CPA-235-05		**Repeat Study: CPA-295-06**	
Parameter	**Test**	**Reference**	**Test**	**Reference**
Cmax (ng/mL)	**4.554 (32.33%)**	**4.972 (33.03%)**	**4.731 (24.35%)**	**4.807 (23.03%)**
AUC 0-t (ng·hr/mL)	**266.01 (36.71%)**	**269.72 (37.85%)**	**269.45 (30.70%)**	**257.19 (32.13%)**
AUC 0-∞ (ng·hr/mL)	**283.23 (36.94%)**	**286.57 (37.66%)**	**286.74 (31.25%)**	**274.13 (33.90%)**
Tmax Median (hr)	**11.09 (62.31%)**	**7.17 (25.59%)**	**8.00 (4.00 – 12.03)**	**8.00 (5.00-12.00)**
T ½ (hr)	**45.12 (25.90%)**	**45.40 (26.78%)**	**43.60 (22.17%)**	**44.54 (22.68%)**
Kel (hr)	**0.0165 (28.73%)**	**0.0163 (25.74%)**	**0.0166 (21.69%)**	**0.0164 (23.78%)**

- **The point estimates for AUC_{0-t}, AUC_{0-inf} and Cmax for the two studies should be within 15%:** The point estimates for AUC_{0-t}, AUC_{0-inf} and Cmax for the two studies is within 15% (Table 10).

Table 10: Comparison of the Studies

COMPARISON OF THE STUDIES				
	Original Study: CPA-235-05		**Repeat Study: CPA-295-06**	
	Test (Repeat)/Test (Original)		**Ref (Repeat)/Ref (Original)**	
Cmax (ng/mL)	**4.731/4.554**	**103.89%**	**4.807/4.972**	**96.68%**
AUC 0-t (ng(hr/mL)	269.45/266.01	101.29%	257.19/269.72	95.35%
AUC 0-∞ (ng(hr/mL)	286.74/283.23	101.24%	274.13/286.57	95.66%
Tmax Median (hr)	8.00/11.09	72.13%	8.00/7.17	111.58%
T ½ (hr)	43.60/45.12	96.63%	44.54/45.40	98.11%
Kel (hr)	0.0166/0.0165	100.61%	0.0164/0.0163	100.61%

F. Discussion

- **Discussion of Tmax:**
  The difference between the Tmax of the TEST and REFERENCE is acceptable in the repeat study. The Tmax difference between the TEST and REFERENCE treatments was not significantly different in the repeat study. The early exposure, AUC0-7h, for the original study has a ratio of 0.864 and the 90% confidence interval of TEST vs. REFERENCE is 81.18% to 91.63%.

- **Biowaiver for 2.5 mg and 5.0 mg orally disintegrating tablets:**
  The dissolution profiles of all strengths are rapid and complete in all media (pH 1.2, pH 4.5 and pH 6.8). The f2 for the 2.5 mg (52.9) and the 5.0 mg (75.7) indicate that the profiles are similar in pH 6.8 buffer. The waiver for the 2.5 mg and 5.0 mg strength is acceptable based on composition proportionality and dissolution profile comparability in pH 1.2, pH 4.5 and pH 6.8 media.

- **Dissolution Specification:**
  The United States Pharmacopeia acceptance criteria for a Q —— is divided into stages. At stage-1, six units are evaluated, at stage-2 twelve units are evaluated and at stage-3 twenty-four units are evaluated. The dissolution must meet the following criteria to be acceptable (Table 11): b(4)

Table 11: USP Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q -15%.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than Q, not more than 2 units are less than Q −15%, and no unit is less than Q −25%.

The stability dissolution results evaluated at S2 (12 units) could have a minimum tablet allowed at ——, and the average of the 12 units would have to be —— There is no tablet less than 74% dissolved in 15 minutes in all of the stability lots tested. The dissolution specification is not set on stability data and all lots are not expected to pass stage-1. This being said, a dissolution specification of Q ——in 15 minutes appears to be appropriate based on the data. b(4) b(4)

- **Evaluation of the repeat fasting BA study and comparison of the results**

The repeat study was conducted using the same protocol as the original study, samples were tested at the same facility, the TEST and REFERENCE products used were from the same lot, subject demographics were similar. The point estimates for AUC 0-t, AUC 0-inf, and Cmax for the two studies were within the 15% requested. Repeat/Original was 103.89% for the test and 96.68% for the reference for Cmax; 101.29% for the test and 95.35% for the reference for AUC 0-t; and 101.24% for the test and 95.66% for the reference for AUC 0-inf.

IV. COMMENTS

A. Comments to the Sponsor

1. Dissolution Method

Please adopt the following dissolution method and specifications as the regulatory method.

Dissolution Method and Specifications

Apparatus:	Paddle Method
RPMs:	50 rpm
Medium:	0.01 M HCl
Volume:	500 mL
Specification:	Q-——in 15 minutes

b(4)

2. Comments to the CMC Review Team

The firm has been requested to incorporate the following dissolution method and specification into their quality control tests.

Apparatus:	Paddle Method
RPMs:	50 rpm
Medium:	0.01 M HCl
Volume:	500 mL
Specification:	Q-—— in 15 minutes

b(4)

V. SIGNATURES

Carol Noory
Reviewer
Division of Clinical Pharmacology 1
Office of Clinical Pharmacology

Date

Patrick Marroum
Team Leader Division of Clinical Pharmacology I
Office of Clinical Pharmacology

Date

CC: NDA 22-026 (DFS)
HFD-110 (HintonD, MarciniakT, HaberM, StockbridgeN)
HFD-860 (MehtaM, UppoorR, MarroumP, NooryC)
ViswanathanCT

VI. APPENDIX:

Clinical Pharmacology Studies Reviewed for Current Submission

Protocol #	Study Title	Study Type
Resubmission		
CPA 295-06	Randomized single dose, two-period, crossover, bioequivalence study comparing Amlodipine 10 mg ODT (Synthon Pharmaceuticals, Inc., USA) to Norvasc® 10 mg Tablets (Pfizer, Inc.,USA) in Healthy Volunteers under Fasting Conditions.	This is a two-way crossover, laboratory-blinded, single dose fasted bioequivalence study.

Clinical Study CSP.US01.ADP.bes.mhy.odt10.003.01

b(4)

TITLE: Randomized single dose, two-period, crossover, bioequivalence study comparing Amlodipine 10 mg ODT (Synthon Pharmaceuticals, Inc., USA) to Norvasc® 10 mg Tablets (Pfizer, Inc.,USA) in Healthy Volunteers under Fasting Conditions.

INVESTIGATOR:

STUDY CENTER:

b(4)

PHARMACOKINETIC and STATISTICAL ANALYSIS:

b(4)

STUDY PERIOD: January 20, 2007 to March 9, 2007

STORAGE PERIOD: 49 days

OBJECTIVE: This study was designed to compare the rate and extent of absorption of amlodipine 10 mg orally disintegrating tablets versus Norvasc® 10 mg tablet in healthy male and female volunteers under fasting conditions.

STUDY DESIGN: This is a two-way crossover, laboratory-blinded, single dose fasted bioequivalence study. Following an overnight fast of at least 10 hours, the subjects received 240 mL of water at 1 hour prior to the drug administration and at 1 hour after the dose. At the time of tablet administration, subjects received the ODT with no co-administered water; subjects receiving the Reference tablet received 240 mL of water concomitantly with the tablet.

Treatment:			
Product	**Test/Reference**	**Manufacturer**	**Batch**
Amlodipine 10 mg ODT	**Test**	**Synthon Pharmaceutical**	**3166101V1 (tablet batch) manufactured 2-15-05 Expire 8/2005**
Norvasc 10 mg Tablet	**Reference**	**Pfizer, Inc.**	**4QL275A (Expires 11/2008)**

b(4)

BLOOD SAMPLE COLLECTION: 8 mL of blood were collected at 0.0 (predose), 0.5 (30 minutes), 1.0*, 2.0, 3.0*, 4.0, 5.0*, 6.0, 7.0, 8.0*, 10.0, 12.0*, 16.0, 24.0*, 32.0*, 48.0*, 72.0*, 96.0*, 144.0*, and 192.0* hours post-dose. Sitting blood pressure and heart rate measurements were taken before dosing and at each * sampling time.

SAFETY ASSESSMENT: Sitting blood pressure and heart rate were measured before dosing and after the drug administration at times marked with a * above. Adverse events were monitored and a physical exam including blood chemistries, hematology and urinalysis were completed prior to dosing and following the final PK sample.

SUBJECTS:
Twenty-six normal healthy, male and female Caucasian subjects (13 males and 13 females) were enrolled in the study. Subjects were between the ages of 19 and 50 years (mean $\pm$ SD = 32.0 $\pm$ 10.1 years). Twenty-six subjects completed the study. 24 subjects were evaluated for bioequivalence assessment and 26 subjects were evaluated for safety analysis.

Demographic Profile of Subjects Completing the Fasting Study

and Included into the PK Evaluation

Data of all subjects included into the statistical evaluation of bioequivalence are presented:

Study No. CSP.US.ADP.be.mby.adf10.003.01			
		Treatment Groups	
		Test Product N =24	Reference Product N =24
Age (years)	Mean ± SD	31.5 ± 2.1	31.5 ± 2.1
	Range	19.0 – 50.0	19.0 – 50.0
Age Groups	< 18	0 (0%)	0 (0%)
	18 – 40	16 (66.7%)	16 (66.7%)
	40 – 64	8 (33.3%)	8 (33.3%)
	65 – 75	0 (0%)	0 (0%)
	> 75	0 (0%)	0 (0%)
Sex	Male	13 (54.2%)	13 (54.2%)
	Female	11 (45.8%)	11 (45.8%)
Race	Asian	0 (0%)	0 (0%)
	Black	0 (0%)	0 (0%)
	Caucasian	24 (100%)	24 (100%)
	Hispanic	0 (0%)	0 (0%)
	Other	0 (0%)	0 (0%)
BMI	Mean ± SD	23.3 ± 0.4	23.3 ± 0.4
	Range	19.1 – 26.8	19.1 – 26.8
Other Factors		-	-

ANALYTICAL METHOD:
A validated HPLC-MS/MS method was employed for the analysis of amlodipine in human plasma. Plasma samples were frozen and stored at -25°C prior to analysis by [redacted] Amlodipine and the internal standard [isotopically labeled (using [redacted] amlodipine] were extracted by solid-phase extraction. An aliquot of this extract was injected into a HPLC system and separated by [redacted] chromatography. The mass spectrometry assay was performed using [redacted]

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Evaluation of the assay was carried out by the construction of an eight point calibration curve covering the range of 0.10 ng/mL to 15.00 ng/mL (in human plasma) and six quality control samples (QCs) at three concentration levels distributed

within one analytical batch. No instability of amlodipine in human plasma at room temperature was observed both under light and dark conditions during 24 hours. A summary of the system performance is given in the following table.

Bioanalytical Method Summary Parameters

ORIGINAL VALIDATION REPORT	
Report Title	Validation Report on an HPLC/MS/MS Method for the Determination of Amlodipine in Human Plasma
Method Description	Solid phase Extraction + HPLC/MS/MS
Method Protocol	VALProt-31-2007
Analytes	Amlodipine (ADP)
Matrix	Plasma-heparin
Method Description	LC/MS/MS
Internal Standard	Tetradeuteroamlodipine
Standard Curve Range	0.10 to 15.00 ng/mL
Matrix Effects	Not Tested.
Selectivity	Acceptable
Benchtop Stability (hours)	24 hours at room temperature
Solutions Stability (days)	47 days at 2 - 8°C
Processed Stability (hours)	142 hours at 20°C
Freeze-Thaw Stability (cycles)	3
Long-term Storage Stability	89 days at ≤ -20°C
Bioanalytical Pre-Validation Report	
Laboratory	[redacted]
Dates of Analysis	February 28, 2007 to March 9, 2007
Report	Determination of amlodipine in human plasma samples, obtained from clinical trial CSP.US.ADP.bes.mhy.odt10.003.01
Report #	151/06
Date	March 26, 2007
Analyst(s)	[redacted]
LLOQ	0.10 ng/mL
Average Drug Recovery	64.3-67.9%
Average Recovery of IS	66.8%
Standard Levels	0.10, 0.30, 1.50, 7.50, 10.00, and 15.00 ng/mL
QC Levels	0.30, 7.50 and 15.00 ng/mL
Intraday Precision	3.0-12.1
Intra day Accuracy	93.3 – 112.6%
Inter day Precision	1.6 -12.8%
Inter day Accuracy	96.4 – 100.5%
Stability -25 °C	49 days
Stability RT	72 hours
Dilution integrity	Concentration diluted 2-fold
Selectivity	No interfering Peaks

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Clinical Runs	
HPLC System	5µm C16, 3 X 50 mm column; acetonitrile: methanol: 2% formic acid water (gradient elution)
MS	Mode: APCI; polarity =positive;
Selective Reaction Monitoring (SRM)	parent m/z 409 to daughter ion m/z 238 (ADP) and parent m/z 413 to daughter ion m/z 238 (dADP)

Quality Control Samples

	Interday Precision	Inter day Accuracy	%Bias
0.30 ng/mL	7.44	98.26	-1.74
5.00 ng/mL	2.83	101.46	1.46
11.00 ng/mL	2.39	100.95	0.95

Calibration Standards

	Interday Precision (%CV)	Inter day Accuracy (% nominal)
0.10 ng/mL	7.14	100.08
0.40 ng/mL	4.67	100.77
1.00 ng/mL	3.29	99.61
3.00 ng/mL	3.68	99.61
6.00 ng/mL	2.88	100.09
9.00 ng/mL	2.47	99.78
12.00 ng/mL	2.23	99.41
15.00 ng/mL	1.83	100.65

PHARMACOKINETICS

Statistical Methods: Using 24 subjects, the statistical power of the study to detect a 20% difference as statistically significant in $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} (ln-transformed) parameters was calculated as 99.99%. Analysis of variance was performed using SAS GLM procedures. The following pharmacokinetic parameters were calculated and statistically analyzed: AUC (0-t), $AUC_{(0-\infty)}$, Cmax, Tmax, kel, and $t_{1/2}$, ln-transformed parameters $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max} and $C_{max}/AUC_{0-\infty}$). The analysis of variance (ANOVA) was performed using the General Linear Model (GLM) procedure, in which the SEQUENCE, SUBJECT (nested in sequence), PERIOD and TREATMENT effects were characterized. The 90% confidence interval of geometric least square means ratio T/R for AUC (0-t), $AUC_{(0-\infty)}$, and Cmax were the primary parameters for the assessment of bioequivalence.

Results:

The summary of the pharmacokinetic parameters for amlodipine geometric mean of non-transformed values are given in the following table.

Pharmacokinetic Results [Mean (± %SD)]

Pharmacokinetic parameter	Amlodipine	Norvasc Amlodipine	Ratio (T/R)	90% CI
AUC (0-t) ng·hr/mL	**269.45 (± 82.73)**	**257.19 (± 82.64**	**104.98**	**101.38-108.70**
AUC (0-inf) ng·hr/mL	**286.74 (± 89.60)**	**274.13 (± 92.22)**	**105.14**	**101.63-108.77**
Cmax (ng/mL	**4.73(± 1.152)**	**4.807 (± 1.107)**	**98.08**	**94.01-102.32**
Tmax (hr)	**8.00 (4.00-12.031)**	**8.00 (5.00-12.00)**	**154.67**	
T ½ (hr)	**43.60 (± 9.67)**	**44.54 (± 10.10)**	**99.36**	
Kel (hr^{-1})	**0.0166 (± 0.00355)**	**0.0164 (± 0.0039)**	**101.20**	
N=24				

The mean data are shown graphically for amlodipine in the following figures.

Figure 4: Amlodipine Plasma Data (N=24)

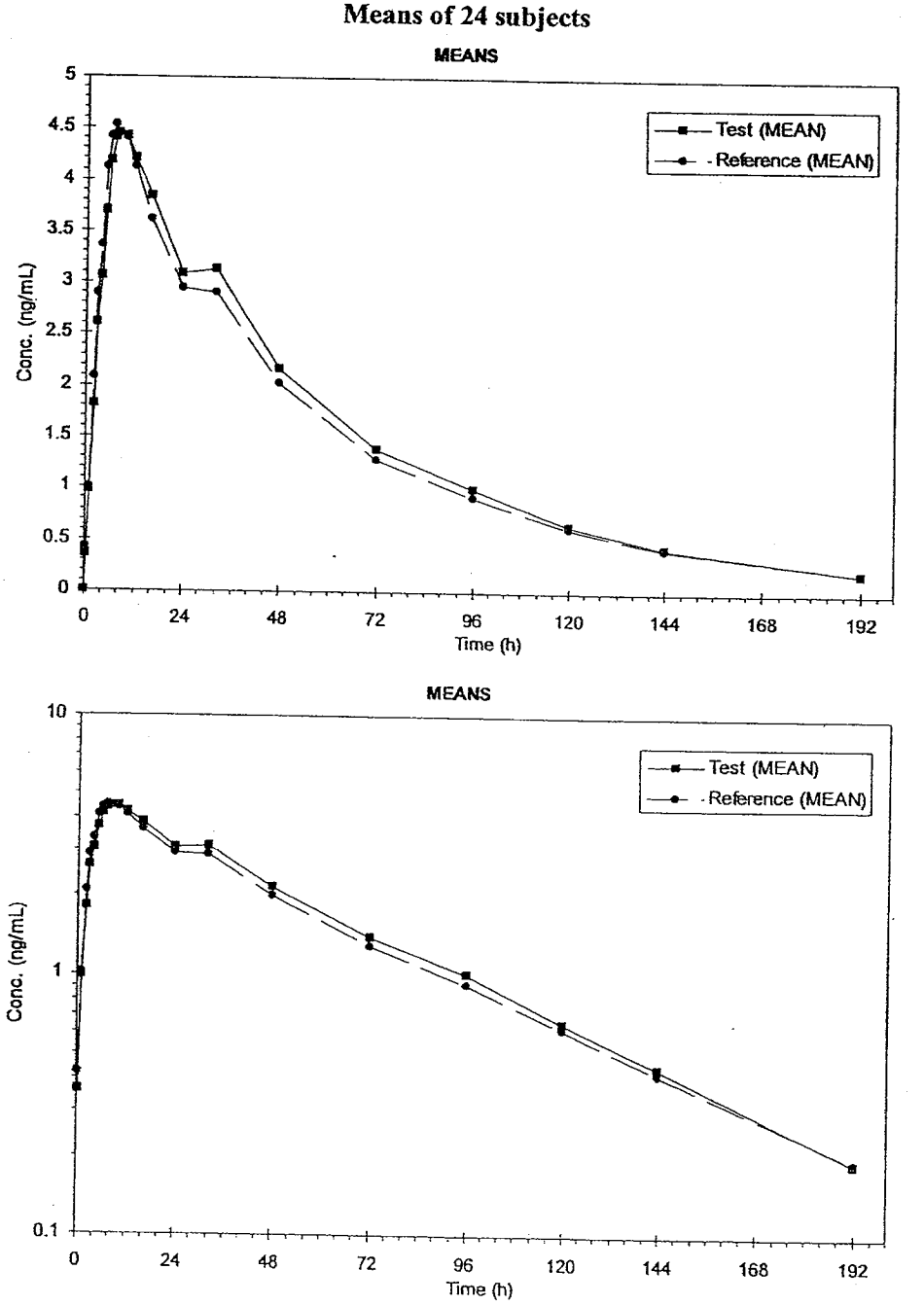
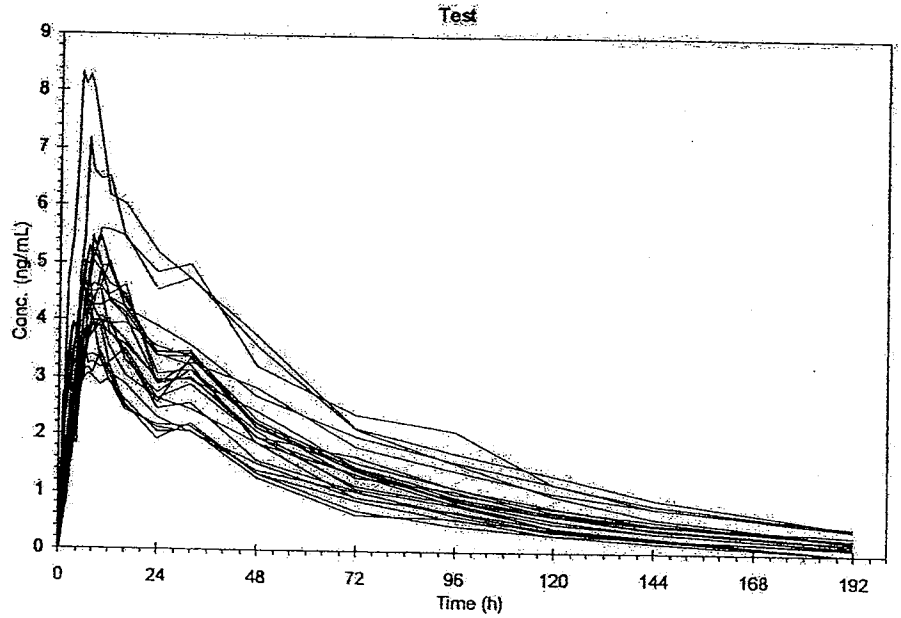


Figure 5: Graphs for all Subjects


Test
Conc. (ng/mL)
Time (h)
0
1
2
3
4
5
6
7
8
9
0
24
48
72
96
120
144
168
192

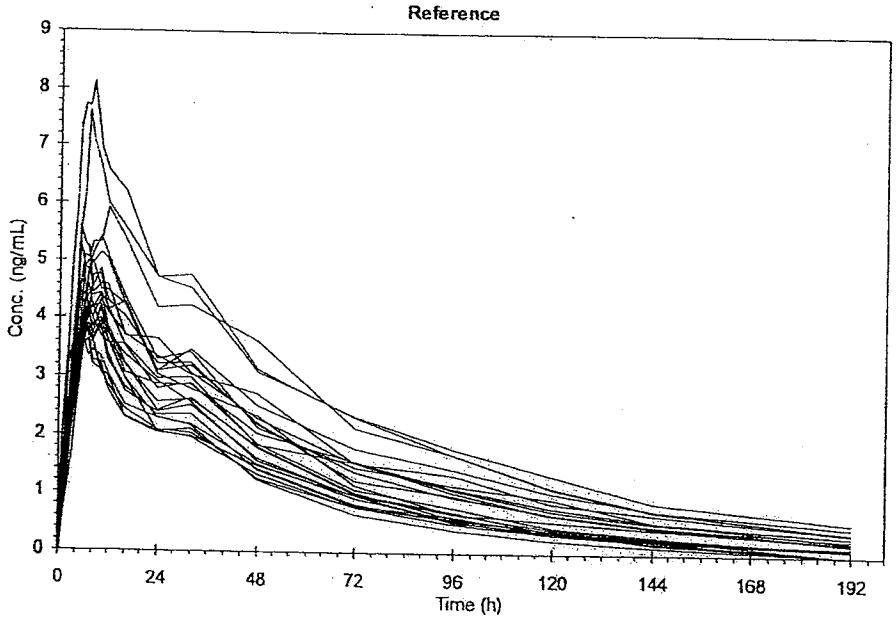
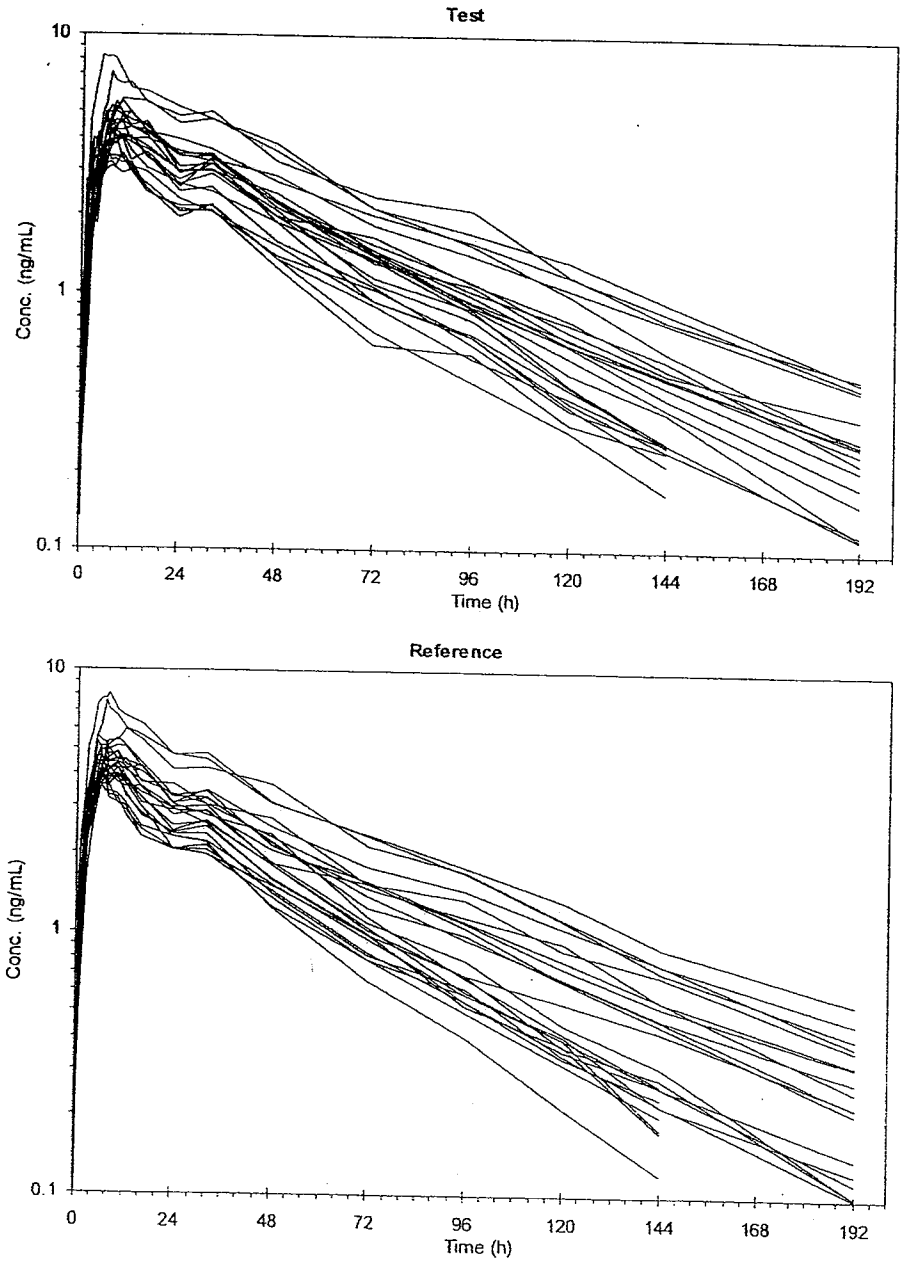

Reference
Conc. (ng/mL)
Time (h)
0
1
2
3
4
5
6
7
8
9
0
24
48
72
96
120
144
168
192

Figure 6: Graphs of all Subjects: Semi logarithmic Scale



SAFETY ASSESSMENT

There were no serious adverse events (AEs) reported. None of the subjects withdrew due to AEs. A total of four AEs were reported by 3 subjects during the study. There were two cases of headache and one case of weakness and common cold. The relationship to the study drug was considered "not" responsible for any of the AEs. No significant safety concerns were raised. A summary of the AEs is shown in the following table.

Incidence of Adverse Events

BODY SYSTEM/ADVERSE EVENT	REPORTED INCIDENCE BY TREATMENT GROUP	
	Test (N=26	Reference (N=26)
General Disorders		
Weakness	0 (0%)	1 (4.2%)
Nervous System Disorders		
Headache	1 (4.2%)	1 (4.2%)
Respiratory Disorders		
Common Cold	1 (4.2%)	0 (0%)
Total	2 (8.3%)	2 (8.3%)

CONCLUSION

1. Based on the statistical results for Amlodipine, the 90% confidence intervals of the least square means based on ln-transformed data for AUC0-t, AUC 0-inf and Cmax of the test compared to the reference formulation was found to be within the range of 80% -125%.
2. The mean of Tmax was 8.00 hours (range 4.00 – 12.03) for the Test formulation and 8.00 hours (range 5.00 – 12.00) for the Reference formulation. .
3. The mean of Kel was 0.0166 hours for the Test formulation and 0.0164 hours for the Reference formulation, while mean t ½ values were 43.60 and 44.54 hours following the same order.

Safety:

There were no serious adverse events reported and no significant safety concerns were raised.

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/s/

Carol Noory
4/25/2007 03:04:29 PM
BIOPHARMACEUTICS

Patrick Marroum
4/25/2007 03:34:52 PM
BIOPHARMACEUTICS

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: March 23, 2006

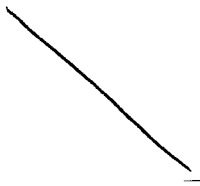
TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

FROM: Carol Noory
Division of Clinical Pharmacology and Biopharmaceutics 1

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-026 (Amlodipine ODT)

Study/Site Identification:

The following studies/sites pivotal to approval have been identified for inspection:

Study #	Clinical Site	Study#	Analytical Site
CPA236-05 CPA235-05		110/236/05 109/235/05	

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Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by July 31, 2006. We intend to issue an action letter on this application by August 31, 2006.

Should you require any additional information, please contact Denise Hinton.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Hinton
4/24/2006 04:25:04 PM