

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-401

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ADDENDUM TO ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-401
Submission Date:	09/25/09 (SDN-
Brand Name:	Twynsta
Generic Name:	Telmisartan/Amlodipine
Formulation:	Fixed dose combination (FDC) immediately release (IR) Tablets
Strength:	80 mg/10 mg, 80 mg/5 mg, 40 mg/10 mg, and 40 mg/5 mg
Sponsor:	Boehringer Ingelheim
Type of submission:	Response to 09/04/09 Information Request
Reviewer:	Tien-Mien Chen, Ph.D.

BACKGROUND

Boehringer Ingelheim (BI) has developed a new Fixed Dose Combination (FDC) product for telmisartan and amlodipine, and submitted NDA 22-401 for review on 12/18/08. Two middle strengths out of the proposed 4 strengths were requested biowaivers using the in vitro comparative dissolution data. The biowaiver request and in vitro comparative dissolution data were reviewed by the Biopharmaceutics group. On 09/04/09, an information request was sent to BI regarding Biopharm comments on dissolution methodology and specification for telmisartan and amlodipine.

REVIEW OF RESPONSES AND DISCUSSIONS:

On 09/25/09, BI submitted their responses to Agency's 09/04/09 information request. BI's responses are further reviewed and they are summarized below.

- 1). BI provided additional dissolution data and requested that the dissolution specification for telmisartan remain the same, i.e., $Q = (b)(4)$ in 30 min instead of the Agency's proposed $Q = (b)(4)$ in 15 min.
- 2). BI requested FDA concurrence that the NDA be approved with their proposed dissolution methodology and specifications for amlodipine, 500 mL 0.01 N HCl, pH 2 using paddle with 75 rpm with a tightened acceptance criteria of Q of $(b)(4)$ at 30 minutes, along with a post approval commitment.

As part of the post approval commitment, BI will provide FDA with necessary data to be generated and an assessment to determine if testing conditions, using the Agency's proposed phosphate buffer pH 6.8, are appropriate. Should the dissolution method using the phosphate buffer at pH 6.8 be deemed suitable, an appropriate specification for amlodipine will be presented along with justification for acceptance criteria.

Please see sponsor's 09/25/09 responses to Agency's 09/04/09 Information Request in Appendix for details.

A t-con was held on 10/02/09 to resolve the above dissolution issues. At the end of the t-con, the sponsor and the Agency agreed that

- For telmisartan, BI proposed a dissolution specification of $Q = \text{(b) (4)}$ in 30 min on an interim basis upon NDA approval. As a post approval commitment, BI will also generate additional dissolution data at 20 min and investigate if $Q = \text{(b) (4)}$ in 20 min is feasible and will submit the data and justifications for review.
- For amlodipine, the sponsor's post approval commitment is acceptable by the Agency and BI's proposed dissolution methodology and specifications will also be used on an interim basis. BI will generate and submit additional dissolution data based on the Agency's proposed dissolution methodology and will propose specifications with justification for review.

RECOMMENDATION:

The agency and BI reached an agreement in a t-con as shown above for a post approval commitment for both telmisartan and amlodipine. Per post approval commitment, the sponsor agreed to submit the new dissolution data along with the proposed new methodology and/or specifications to the Agency for review in one year from the day of issuance of the approval letter. No further comments are to be conveyed to the sponsor.

Tien-Mien Chen, Ph.D.
Reviewer
ONDQA Biopharmaceutics

10/02/09

Date

Patrick Marroum, Ph.D.
ONDQA Biopharmaceutics

10/02/09

Date

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

**NDA 22-401 for Twynsta
(Telmisartan/Amlodipine) FDC, 80 mg/10 mg,
80 mg/5 mg, 40 mg/10 mg, and 40 mg/5 mg
IR Tablets**

Appendix

**BI's 09/25/09 Responses to Agency's 09/04/09
Information Request**

RESPONSE TO FDA INFORMATION REQUEST DATED SEPTEMBER 4, 2009

FDA Request #1:

For telmisartan, the proposed dissolution methodology (900 mL phosphate buffer pH 7.5 using paddle with 75 rpm) is acceptable, but the specifications should be tightened as follows: From $Q = \square^{(b)(4)}$ in 30 min to $Q = \square^{(b)(4)}$ in 15 min.

BI response:

Boehringer Ingelheim (BI) acknowledges FDA's suggestion to tighten the specification for the dissolution of telmisartan. However, the dissolution specification for telmisartan/amlodipine fixed dose combination has been established based on pivotal clinical and registration stability batches. For the following reasons, BI proposes to maintain the specification of Q of $\square^{(b)(4)}$ in 30 minutes.

- The telmisartan dissolution data for the primary stability batches (three batches for each of the four strengths, including the two BE batches) were evaluated at 15 and 30 minutes at batch release. The data are summarized in Table 1. The results at 15 minutes show a lower and incomplete drug dissolution of telmisartan compared to 30 minutes for all strengths and batches. As shown in the table, the batch numbers highlighted with the yellow color would have required Stage 2 testing based on the results of the 15 minute time point and a Q of $\square^{(b)(4)}$. Although Stage 3 testing was not actually performed, the two batch numbers highlighted with the red color, would most likely have failed an acceptance criteria of Q of $\square^{(b)(4)}$ at 15 minutes.
- The proposed acceptance criteria for dissolution of telmisartan from telmisartan/amlodipine tablets is identical to or tighter than approved dissolution specification for the market products telmisartan (Micardis®) tablets and telmisartan/hydrochlorothiazide (Micardis HCT®) tablets, respectively. The approved specifications for telmisartan tablets and telmisartan/hydrochlorothiazide tablets are Q of $\square^{(b)(4)}$ and Q of $\square^{(b)(4)}$ at 30 minutes, respectively. The composition and manufacturing process of the telmisartan layer of telmisartan/amlodipine tablets are identical to these market products. BI has extensive manufacturing and dissolution testing experience for these established products. The proposed specification of Q of $\square^{(b)(4)}$ in 30 minutes will allow BI to maintain a historical perspective and bridge our prior manufacturing experience to ensure the quality of the telmisartan/amlodipine drug product.

FDA concurrence with this proposal is requested.

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FDA Request #2:

For amlodipine, the proposed dissolution methodology (500 mL 0.01 N HCl pH 2 using paddle with 75 rpm) and specifications ($Q = \text{[redacted]}^{(b)(4)}$ in 30 min) are not acceptable, since $\text{[redacted]}^{(b)(4)}$ dissolved in 10 min. Therefore, the following dissolution methodology and specifications should be implemented:

*Apparatus: Paddle (USP Apparatus II) with 75 rpm
Medium: 900 mL phosphate buffer (pH 6.8) at 37°C
Specifications: $Q = \text{[redacted]}^{(b)(4)}$ in 15 min*

BI response:

Boehringer Ingelheim (BI) acknowledges FDA's suggestion to modify the dissolution methodology, however, BI has not collected extensive batch release or any stability data using the proposed dissolution medium of pH 6.8. BI will commit to generate the necessary data post approval to determine if the method is appropriate for the product. We propose to collect stability data on the primary stability batches at 36 months as well as the ongoing stability for the first three production batches at 18 months per the post approval stability commitment, using both the dissolution media 0.01 N HCl at pH 2 and phosphate buffer at pH 6.8. As part of the post approval commitment, BI will provide FDA with the data and an assessment as to whether the testing conditions using phosphate buffer, pH 6.8 are appropriate for determination of amlodipine dissolution in telmisartan/amlodipine tablets. Should the dissolution method using the phosphate buffer at pH 6.8 be deemed suitable, an appropriate specification will be presented along with justification for acceptance criteria.

BI requests FDA concurrence that the NDA be approved with the proposed dissolution methodology for amlodipine, 500 mL 0.01 N HCl, pH 2 using paddle with 75 rpm with a tightened acceptance criteria of Q of $\text{[redacted]}^{(b)(4)}$ at 30 minutes, along with the above post approval commitment.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22401

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

TELMISARTAN/AMLODIPINE
FIXED DOSE COM TB

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/s/

TIEN MIEN CHEN
10/05/2009

PATRICK J MARROUM
10/05/2009

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-401
Submission Date:	12/18/08
Brand Name:	Twynsta
Generic Name:	Telmisartan/Amlodipine
Formulation:	Fixed dose combination (FDC) immediately release (IR) Tablets
Strength:	80 mg/10 mg, 80 mg/5 mg, 40 mg/10 mg, and 40 mg/5 mg
Sponsor:	Boehringer Ingelheim
Type of submission:	Biowaiver request for 2 middle strengths (80 mg/5 mg and 40 mg/10 mg)
Reviewer:	Tien-Mien Chen, Ph.D.

BACKGROUND

Both Micardis (telmisartan) tablets 40 and 80 mg (NDA 20-850) and Norvasc (amlodipine) 5 and 10 mg tablets (NDA 19-787) are the approved single-entity products in the US. Boehringer Ingelheim has developed Fixed Dose Combination (FDC) products with telmisartan and amlodipine as drug substances. The telmisartan/amlodipine tablets were developed as layered IR tablets in four strengths, 80 mg/10 mg, 80 mg/5 mg, 40 mg/10 mg and 40 mg/5 mg.

Bioequivalence (BE) studies were reportedly performed successfully between the FDC products telmisartan/amlodipine 40/5 mg (lowest strength) and telmisartan/amlodipine 80/10 mg (highest strength) and the corresponding strengths of the single-entity products.

Only two of the four strengths were tested *in vivo* and other two middle strengths were requested for biowaivers using the *in vitro* comparative dissolution data. This bracketing design was accepted by the FDA in a general correspondence dated 08/10/07. The biowaiver request and *in vitro* comparative dissolution data are therefore, reviewed here.

FORMULATION COMPARISONS

The sponsor reported that four strengths of the telmisartan/amlodipine FDC tablets are proportionally similar:



The composition/formulation of telmisartan/amlodipine layered FDC tablets are shown below.

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22401	----- ORIG 1	----- BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	----- TELMISARTAN/AMLODIPINE FIXED DOSE COM TB

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/s/

TIEN MIEN CHEN
08/31/2009

PATRICK J MARROUM
08/31/2009

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-401
Submission Date: December 18, 2008
Generic Name: Telmisartan (T)/Amlodipine (A)
Brand Name (proposed): Twynsta[®] Tablets
Applicant: Boehringer Ingelheim
Dosage Form, Strength: Tablet: T/A 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg
Indication: Hypertension
DCP: Clinical Pharmacology 1
OND: Cardiovascular and Renal Drug Products

Primary Reviewer: Islam R. Younis, Ph.D.
Team Leader (Acting): Angelica Dorantes, Ph.D.

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1.0 Executive Summary

Background

Boehringer Ingelheim submitted NDA 22-401 for Twynsta[®] (Telmisartan/Amlodipine) Tablets on December 18, 2008. The applicant is seeking approval for the fixed dose combination (FDC) tablet for the treatment of hypertension. The applicant is planning on marketing the FDC tablets in the following dosage strengths: telmisartan/amlodipine 40/5 mg, 40/10 mg, 80/5 mg/ and 80/10 mg.

Clinical Pharmacology/Biopharmaceutics Findings

1. The lowest strength of the fixed dose combination tablet of telmisartan/amlodipine (40/5 mg) is bioequivalent to the individual Micardis[®] (telmisartan) 40mg tablets and US-Norvasc[®] (amlodipine) 5 mg tablets.
2. The highest strength of the fixed dose combination tablet of telmisartan/amlodipine (80/10 mg) is bioequivalent to the individual Micardis[®] (telmisartan) 80mg and US-Norvasc[®] (amlodipine) 10 mg tablets.
3. The exposure ($AUC_{0-24,ss}$ and $C_{max,ss}$) of telmisartan is not affected by concomitant administration of amlodipine. Similarly, the exposure of amlodipine is not affected by co-administration of telmisartan.
4. When the FDC tablet is ingested with a high fat meal, food significantly reduces telmisartan $AUC_{0-\infty}$ and C_{max} by 24.3% and 60.1% respectively. However, food does not affect the exposure of amlodipine

RECOMENDATION

The Office of Clinical Pharmacology (OCP) has reviewed Original NDA 22-401 for Twynsta Tablets.

Clinical Pharmacology: OCP finds the clinical pharmacology and biopharmaceutical information submitted under NDA 22-401 acceptable, provided the audit reports from the Division of Scientific Investigations for the pivotal bioequivalence studies No. 1235.3 and 1235.4 are satisfactory. There are no Phase IV commitments.

Labeling: The proposed labeling does not include information for the effect that food has on telmisartan's C_{max} (60% decrease). Therefore, sections 2.1 (Dosage and Administration) and 12.3 (Pharmacokinetics) of the proposed labeling should be revised as appropriate.

Islam R. Younis, Ph.D.
Division of Clinical Pharmacology 1

Date: 05/07/2009

Office of Clinical Pharmacology

FT signed by:
Angelica Dorantes, Ph.D. (Acting Team Leader)

Date: 05/08/2009

cc: NDA 22-401, HFD 110 (NguyenQ), HFD-860 (Younis, Mehta, Uppoor)

Clinical Pharmacology Briefing: May 6, 2009

Attendants: Mehul Mehta, Ramana Uppoor, Angelica Dorantes, Norman Stockbridge,
Thomas Marciniak, Melanie Blank, Ting Ong, Divya Menon-Andersen, and Islam Younis

2.0 Question Based Review

An abbreviated version of the QBR is been adapted for the review of this NDA, since key QBR elements have been addressed previously during the review of NDA 20-850 for Micardis[®] (telmisartan) Tablets and NDA 19-787 for US-Norvasc[®] (amlodipine) Tablets.

Telmisartan is available in the US as Micardis[®] tablets for oral administration in three dose strengths (20 mg, 40 mg, 80 mg), and was approved under NDA 20-850 on November 10, 1998. Amlodipine besylate is available in the US as Norvasc[®] tablets for oral administration in three dose strength (2.5, 5, and 10mg), and was approved under NDA 19-787 on July 31, 1992.

The current NDA includes data to support the approval of telmisartan/amlodipine fixed dose combination tablets. This submission includes; one pivotal clinical trial and five Phase I studies (i.e., two bioequivalence studies, two drug-drug interaction studies, and one food effect study). The safety package for this application includes data from multiple supportive clinical trials.

2.1 General attributes of drug product

Boehringer Ingelheim submitted NDA 22-401 for telmisartan/amlodipine fixed dose combination tablets on December 18, 2008. The sponsor plans on marketing the fixed dose combination tablets under the proposed trade name Twynsta[®] with the following dosage strengths: telmisartan/amlodipine 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg. The applicant is seeking approval for the treatment of hypertension.

2.1.1. What are the highlights of the formulation of the drug product?

The composition for the formulations of the different strengths of the telmisartan/amlodipine fixed dose combination tablets are shown in the table below:

Ingredients	Function	Tablet Strength (A/D)			
		40/5	40/10	80/5	80/10
		mg/tablet			
Telmisartan layer					
Telmisartan	Drug substance	40.0	40	80	80
Sodium hydroxide	(b) (4)				
Povidone (b)					
Meglumine					
(b) (4)					
Sorbitol					
Magnesium stearate					(b) (4)
<hr/>					
Amlodipine besylate (1)	Drug substance	6.935	13.87	6.935	13.87
Microcrystalline cellulose	(b) (4)				
Pregelatinized starch					
Corn starch					
Colloidal silicon dioxide					
(b) (4)					
Magnesium stearate					(b) (4)
<hr/>					
Total weight of layered tablet		440.0	440	680.0	680.0

2.1.2. What are the proposed mechanism of action and therapeutic indication of telmisartan and amlodipine?

Telmisartan is a nonpeptide second generation Type I angiotensin II receptor (type AT₁) antagonist. Telmisartan selectively inhibits the pressor effects of the renin-angiotensin-aldosterone system.

Amlodipine is a calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The fixed dose combination product is indicated for the treatment of hypertension.

2.1.3. What is the proposed dosage and route of administration?

Telmisartan is effective for the treatment of hypertension in once daily doses of 20-80 mg while amlodipine is effective in doses of 2.5-10 mg. Dosage must be individualized and may be increased after at least 2 weeks. Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks. The maximum recommended dose of Twynsta[®] tablets is 80/10 mg once daily.

Because of decreased clearance of amlodipine, therapy should usually be initiated with 2.5 mg in patients 75 years or older.

The available dosage strengths of Twynsta® (telmisartan/amlodipine) tablets are; 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg. The route of administration is oral.

2.2 General clinical pharmacology

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

Telmisartan/amlodipine clinical development program is primarily based on the pivotal clinical study No. 1235.1. This study is randomized, double-blind, double-dummy, placebo-controlled, parallel group, 8-week 4 x 4 factorial design comparison of 16 treatments (placebo, telmisartan monotherapy (20, 40, and 80 mg), amlodipine monotherapy (2.5, 5, and 10 mg) to evaluate the efficacy and safety of telmisartan/amlodipine combination in patients with stage I or II hypertension.

The clinical pharmacology section of the submission contained the following studies:

1. One food effect study (No. 1235.12,)
2. Two bioequivalence studies (No. 1235.3 and 1235.4)
3. Two drug-drug interaction studies (No. 1235.2 and 502.126)

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint was change from baseline in the in-clinic seated trough cuff diastolic blood pressure after eight weeks of treatment. This is a typical endpoint for hypertension efficacy studies.

2.3 Intrinsic Factors

The intrinsic factors were not evaluated in this NDA. The intrinsic factors for the individual components telmisartan and amlodipine were previously described in the corresponding CP reviews of these submissions.

2.4 Extrinsic Factors

2.4.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

There are no *in vitro* basis to suspect drug-drug interactions between amlodipine and telmisartan.

Studies 1235.2 and 502.126 evaluated the pharmacokinetic interactions of amlodipine and telmisartan at steady state.

Study 1235.2 - Effect of amlodipine on telmisartan: The systemic exposure of telmisartan at steady state ($AUC_{0-24,ss}$ and $C_{max,ss}$) is not affected by co-administration of amlodipine (steady state), as shown in the table below:

Parameter	Geometric Mean (%CV)				Ratio % (T+A)/T	90% CI	
	N	(T+A)	N	(T alone)		Lower	Upper
$AUC_{0-24,ss}$ (ng h/mL)	36	99.9 (95.1)	36	1023 (74.0)	97.6	89.5	106.5
$C_{max,ss}$ (ng/mL)	36	242 (118)	36	272 (105)	89.0	76.3	103.8

Study 502.126 - Effect of telmisartan on amlodipine: The systemic exposure of amlodipine at steady state ($AUC_{0-24,ss}$ and $C_{max,ss}$) is not affected by co-administration of telmisartan (steady state), as shown in the table below:

Parameter	Geometric Mean (%CV)				Ratio % (T+A)/A	90% CI	
	N	(T+A)	N	(A alone)		Lower	Upper
$AUC_{0-24,ss}$ (ng.h/mL)	12	352 (30.9)	12	331 (32.1)	106	97.5	116
$C_{max,ss}$ (ng/mL)	12	18.7 (29.6)	12	17.7 (29.6)	106	97.5	115

2.4.4 What other co-medications are likely to be administered to the target population?

No drug interaction studies were conducted with Twynsta tablets and other drugs. Drug interaction studies were previously conducted with the individual telmisartan and amlodipine components. These drug interactions are included in Twynsta's labeling.

2.5 General Biopharmaceutics

2.5.1 Is the proposed to-be-marketed fixed dose formulation bioequivalent to the individual telmisartan and amlodipine formulations?

Studies No. 1235.3 and 1235.4 evaluated the bioequivalence of the highest and lowest fixed dose combination tablets with respect to the individual tablets, respectively.

Study 1235.3 evaluated the bioequivalence of telmisartan/amlodipine 40/5 mg tablet vs. the individual telmisartan 40 mg and amlodipine 5 mg tablets. This was an open-label, randomized, single-dose, two period, crossover study conducted in 84 subjects (42 males and 42 females).

The results showed no statistically significant difference in telmisartan and amlodipine systemic exposures ($AUC_{0-\infty}$ and C_{max}) between the fixed dose combination (FDC) and the individual tablets (Micardis[®], 40 mg and US-Norvasc[®], 5 mg), as shown in the table below:

	Parameter	N	Geometric Mean (%CV)		Ratio %	90% CI		
			FDC T/A 40/5mg	N		Micardis [®] 40 mg	T/R	Lower
Telmisartan	$AUC_{0-\infty}$ (ng h/mL)	83	630 (82.3)	79	643(80.2)	98.0	92.3	104
	C_{max} (ng/mL)	83	62.0 (83.9)	82	58.5 (66.4)	106	95.8	118
Amlodipine	Parameter	N	Geometric Mean (%CV)		T/R	Lower	Upper	
			FDC T/A 40/5 mg	N				Norvasc [®] 5 mg
	$AUC_{0-\infty}$ (ng h/mL)	84	137(29.9)	83	137 (29.9)	100	98.1	103
	C_{max} (ng/mL)	84		83		100	97.3	103
			2.48 (28.3)		2.48 (26.1)			

Study 1235.4 evaluated the bioequivalence of the highest strength telmisartan/amlodipine 80/10 mg tablets vs. the individual telmisartan 80 mg and amlodipine 10 mg tablets. This was an open-label, randomized, single-dose, two period, crossover study conducted in 84 subjects (42 males and 42 females).

The results showed no statistically significant difference in telmisartan and amlodipine systemic exposures ($AUC_{0-\infty}$ and C_{max}) between the fixed dose combination and the individual tablets (Micardis[®], 80 mg and US-Norvasc[®], 10 mg). The results are summarized in the table below:

	Parameter	N	Geometric Mean (%CV)		Ratio %	90% CI		
			FDC T/A 80/10 mg	N		Micardis [®] 80 mg	T/R	Lower
Telmisartan	$AUC_{0-\infty}$ (ng h/mL)	82	975 (73.3)	83	944 (76.5)	103	98.6	108
	C_{max} (ng/mL)	82	204 (95.3)	83	188 (101)	108	97.7	120
Amlodipine	Parameter	N	Geometric Mean (%CV)		T/R	Lower	Upper	
			FDC T/A 80/10 mg	N				Norvasc [®] 10 mg
	$AUC_{0-\infty}$ (ng h/mL)	82	313 (28.6)	83	297 (25.1)	106	103	108
	C_{max} (ng/mL)	82	6.11 (25.5)	83	5.94 (22.0)	103	101	105

2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?

Study 1235.12 evaluated the effect of food on the bioavailability of telmisartan/ amlodipine 80/10 mg FDC formulation. The results showed that food significantly reduces telmisartan AUC_{0-∞} and C_{max} by 24.3% and 60.1% respectively (see table below and Figure 1). Median T_{max} under fed conditions (2.0 h, range 0.5 -12.0) was higher than that observed under fast conditions (0.98 h, range 0.5 - 2.5).

Parameter	<u>Telmisartan</u>		Ratio % Fed/Fast	90% CI	
	<u>Geometric Mean (% CV)</u>			Lower	Upper
	Fast	Fed			
AUC _{0-∞} (ng h/mL)	1210 (82.9)	912 (72.9)	75.7	71.2	80.5
C _{max} (ng/mL)	192 (99.6)	77.2 (76.5)	39.9	33.1	48.1

However, food does not affect the systemic exposure of amlodipine, as shown in the table below:

Parameter	<u>Amlodipine</u>		Ratio % Fed/Fast	90% CI	
	<u>Geometric Mean (% CV)</u>			Lower	Upper
	Fast	Fed			
AUC _{0-∞} (ng.h/mL)	331 (32.5)	351 (30.2)	108	104	112
C _{max} (ng/mL)	6.54 (29.9)	6.77 (25.0)	104	100	109

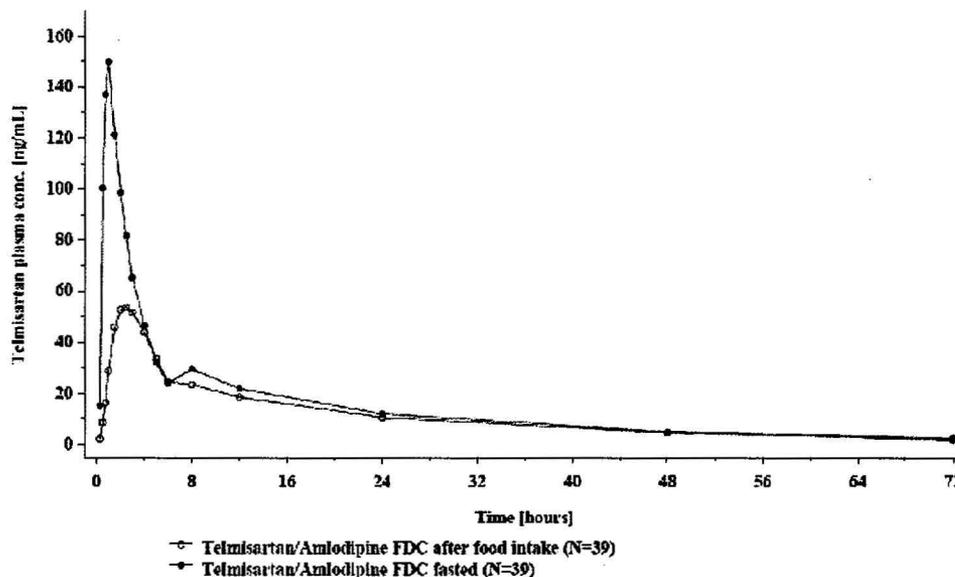


Figure 1. Telmisartan plasma concentration-time profile following the administration of a single oral dose of telmisartan (80mg) and amlodipine (10mg) fixed dose combination under fast and fed conditions.

2.6 Analytical Section

A brief summary of the different bioanalytical methods used is shown in the table below. Accepted validation indicates that method met the FDA guidance “Bioanalytical Method Validation” recommendations. Accepted study samples performance indicates that the quality control samples accuracy and precision met the guidance recommendations. Please refer to the individual studies review and analytical methods review for more details.

Study #	Analyte(s)	Type	Matrix	(b) (4)	Method Validation	Study Sample Performance
502.126	Amlodipine	GC-MS	Plasma		NAv.	Acc.
1235.12	Amlodipine	LC-MS/MS	Plasma		Acc.	Acc.
1235.2						
1235.3						
1235.4						
1235.12	Telmisartan	ELISA	Plasma		Acc.	Acc.
1235.2						
1235.3						
502.126	Telmisartan	HPLC-fluorescence	Plasma		NAv.	Acc.
1235.4	Telmisartan	HPLC-fluorescence	Plasma		Acc.	Acc.

NAv.: No Available, Acc.: Acceptable

3. Detailed Labeling Comments

- The edits/revisions for the proposed labeling will be discussed during the labeling meetings.
- The effect that food has in telmisartan's C_{max} should be included in the labeling. The 2nd paragraph of section "12.3 Pharmacokinetics", should be revised as follows:

After administering TWYNSTA 80/10 mg tablet with a high-fat meal, the total area under the plasma concentration-time curve (AUC) and C_{max} for telmisartan decreased by about 24% and 60%, respectively. For amlodipine, AUC and C_{max} were not altered [*see Dosage and Administration (2.1)*].

- Section "2.1 Dosage and Administration", should clearly indicate if Twysnta Tablets must be taken with or without food.

4.2 Individual Study Review

Bioequivalence Study No. 1235.3

Report #	1235.3
Investigator	Sybille Baumann, M.D.
Study Site	(b) (4)
Study Period	09/28/2007- 11/28/2007

Title

Bioequivalence of 40 mg telmisartan/5 mg amlodipine fixed dose combination compared with its monocomponents in healthy male and female volunteers. An open-label, randomized, single-dose, two-period cross-over study

Objectives

To demonstrate the bioequivalence of 40 mg telmisartan / 5 mg amlodipine fixed dose combination vs. its monocomponents.

Study Subjects

Eight four subjects (42 males and 42 females) participated in the study with mean age of 36.6 ± 8.2 years. All subjects completed the study.

Study Design

This is an open-label, randomized, single-dose, two-period cross-over study. During each treatment period blood sampling was performed over seven days followed by a 14 day washout period between treatments.

Study Drugs

Test Drug: Telmisartan /amlodipine (40/5 mg, Batch # B071002436), fixed dose combination tablet.

Reference Drugs:

1. Telmisartan 40 mg tablets (Micardis[®], batch # B061002392)
2. Amlodipine 5 mg tablets (US-Norvasc[®], batch # B071001222)

Both test and reference drugs were administered with 240 mL water after an overnight fast.

Pharmacokinetic Blood Sampling

Venous blood samples were collected at the following times:

1. Telmisartan: At pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose.
2. Amlodipine: At pre-dose and at 0.5, 1, 2, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 post-dose.

Assay Method

Telmisartan: An ELISA method was used for the quantification of telmisartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.03 – 30 ng/mL with LLOQ of 0.3 ng/mL (%CV ≤ 3.7, %RE: -3.5 – 5.1). The precision of the quality control samples was ≤ 6.8% and the accuracy was -8.4% – 0.3%.

Amlodipine: A validated HPLC-MS/MS method was used for the quantification of amlodipine in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.05 – 10 ng/mL with LLOQ of 0.05 ng/mL (%CV ≤ 9.8, %RE: -4.0 – 4.4). The precision of the quality control samples was ≤ 3.9 % and the accuracy was – 3.8% – 1.1%.

Pharmacokinetics Data Analysis

Telmisartan and amlodipine primary PK parameters (C_{max} and $AUC_{0-\infty}$) and secondary parameters (AUC_{0-168} , T_{max} , $t_{1/2}$, CL/F , and V_z/F) were computed by standard non-compartmental method of analysis

Statistical Method

A mixed-effect analysis of variance (ANOVA) model on log transformed parameters was used to compare the pharmacokinetic parameters of amlodipine and telmisartan for each treatment period. Two-sided 90% confidence intervals (CIs) for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of $AUC_{0-\infty}$ and C_{max} were calculated.

Results

Telmisartan:

There was no statistically significant difference in telmisartan systemic exposure between the fixed dose combination and the individual innovator tablets (Micardis®), as shown in the table below:

Parameter	<u>Geometric Mean (%CV)</u>				<u>Ratio %</u>	<u>90% CI</u>	
	N	Test	N	Reference	T/R	Lower	Upper
$AUC_{0-\infty}$ (ng h/mL)	83	630 (82.3)	79	643 (80.2)	98.0	92.3	104.1
C_{max} (ng/mL)	83	62.0 (83.9)	82	58.5 (66.4)	106.1	95.8	117.5

Amlodipine:

There was no statistically significant difference in amlodipine systemic exposure between the fixed dose combination and the individual innovator tablets (US-Norvasc[®]), as shown in the table below:

Parameter	Geometric Mean (%CV)				Ratio % T/R	90% CI	
	N	Test	N	Reference		Lower	Upper
AUC _{0-∞} (ng h/mL)	84	137 (29.9)	83	137 (29.9)	100.4	98.1	102.7
C _{max} (ng/mL)	84	2.48 (28.3)	83	2.48 (26.1)	100.0	97.3	102.7

Safety

No death or any other serious adverse events occurred during this study.

Conclusions

The fixed dose combination tablet of telmisartan/ amlodipine (40/5 mg) is bioequivalent to the individual innovator tablet Micardis[®] (telmisartan 40mg) and US-Norvasc[®] (amlodipine 5 mg).

Bioequivalence Study 1235.4

Report #	1235.4
Investigator	Mario Iovino, M.D.
Study Site	Boehringer Ingelheim Pharma GmbH & Co. KG 88397 Biberach, Germany
Study Period	09/12/2007- 11/14/2007

Title

Bioequivalence of 80 mg telmisartan/10 mg amlodipine fixed dose combination compared with its monocomponents in healthy male and female volunteers. An open-label, randomized, single-dose, two-period cross-over study

Objectives

To demonstrate the bioequivalence of 80 mg telmisartan /10 mg amlodipine fixed dose combination vs. its monocomponents.

Study Subjects

Eight four subjects (42 males and 42 females) participated in the study with mean age of 36.7 ± 9.2 years.

Study Design

This is an open-label, randomized, single-dose, two-period cross-over study. During each treatment period blood sampling was performed over seven days followed by a 14 day washout period between treatments.

Study Drugs

Test Drug: Telmisartan /amlodipine (80/10 mg, Batch # B071002436), fixed dose combination tablet.

Reference Drugs:

1. Telmisartan 80 mg tablets (Micardis[®], batch # B061000323)
2. Amlodipine 10 mg tablets (US-Norvasc[®], batch # B071001223)

Both test and reference drugs were administered with 240 mL water after an overnight fast.

Pharmacokinetic Blood Sampling

Venous blood samples were collected:

1. Telmisartan: At pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose.
2. Amlodipine: At pre-dose and at 0.5, 1, 2, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 post-dose.

Assay Methods

Telmisartan: An HPLC-fluorescence method was used for the quantification of telmisartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.5 – 400 ng/mL with LLOQ of 0.5 ng/mL (%CV \leq 4.6, %RE: -1.5 – 2.4). The precision of the quality control samples was \leq 4.2% and the accuracy was -1.9% – 2.5%.

Amlodipine: A validated HPLC-MS/MS method was used for the quantification of amlodipine in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.05 – 10 ng/mL with LLOQ of 0.05 ng/mL (%CV \leq 9.8, %RE: -0.3 – 2.7). The precision of the quality control samples was \leq 4.5% and the accuracy was -1.7% – 3.4%.

Pharmacokinetics Data Analysis

Telmisartan and amlodipine primary PK parameters (C_{\max} and $AUC_{0-\infty}$) and secondary parameters (AUC_{0-168} , T_{\max} , $t_{1/2}$, CL/F , and V_z/F) were computed by standard non-compartmental methods of analysis

Statistical Method

A mixed-effect analysis of variance (ANOVA) model on log transformed parameters was used to compare the pharmacokinetic parameters of amlodipine and telmisartan for each treatment period. Two-sided 90% confidence intervals (CIs) for the intra-subject test to reference ratio (as estimated by the ratio of the geometric means) of each of $AUC_{0-\infty}$ and C_{\max} were calculated.

Results

Three (from 84) subjects were discontinued the study:

1. Subjects No. 83 and 84 (both female) discontinued due to adverse events before visit 3.
2. Subject No. 78 discontinued due to missing venous puncture at visit 3 before dosing.

Telmisartan:

There was no statistically significant difference in telmisartan systemic exposure between the fixed dose combination and the individual innovator tablets (Micardis®), as shown in the table below:

Parameter	Geometric Mean (%CV)				Ratio % T/R	90% CI	
	N	Test	N	Reference		Lower	Upper
AUC _{0-∞} (ng h/mL)	82	975 (73.3)	83	944 (76.5)	103.3	98.6	108.3
C _{max} (ng/mL)	82	204 (95.3)	83	188 (101)	108.2	97.7	119.7

Amlodipine:

There was no statistically significant difference in amlodipine systemic exposure between the fixed dose combination and the individual innovator tablets (US-Norvasc®), as shown in the table below:

Parameter	Geometric Mean (%CV)				Ratio % T/R	90% CI	
	N	Test	N	Reference		Lower	Upper
AUC _{0-∞} (ng h/mL)	82	313 (28.6)	83	297 (25.1)	105.6	103.3	107.9
C _{max} (ng/mL)	82	6.11 (25.5)	83	5.94 (22.0)	102.9	100.5	105.4

Safety

No death or any other serious adverse events occurred during this study.

Conclusions

The fixed dose combination tablet of telmisartan/ amlodipine (80/10 mg) is bioequivalent to the individual innovator tablet Micardis® (telmisartan 80mg) and US-Norvasc® (amlodipine 10 mg) administered simultaneously.

Drug-Drug Interaction Study No. 1235.2

Report #	1235.2
Investigator	Ulrich Feifel, M.D.
Study Site	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Clinical Research Human Pharmacology Centre, Birkendorfer Strasse 65 88397 Biberach an der Riss, Germany
Study Period	05/22/2006 - 08/21/2006

Title

Pharmacokinetics of repeated oral doses of 80 mg telmisartan (Micardis[®]) at steady state alone and in combination with repeated oral doses of amlodipine 10 mg (Norvasc[®]) at steady state. A two-way crossover, open, randomized design study

Objectives

To investigate the steady state pharmacokinetics of 80 mg telmisartan alone and in combination with repeated doses of 10 mg amlodipine

Study Rationale

Telmisartan and amlodipine will be used in a fixed dose combination tablet, and the current study will evaluate the effect of amlodipine on the steady state pharmacokinetics of telmisartan.

Study Subjects

Thirty-eight subjects (18 males and 20 females) participated in the study with mean age of 37.7 ± 7.2 years. All subjects completed the study.

Study Design

This is an open-label, randomized, two-way cross-over study in healthy volunteers. The study design is illustrated in the scheme below:

Day	1	2	3	4	5	6	7	8	9		1	2	3	4	5	6	7	8	9
sequence 1	Telmisartan alone 80 mg qd									Washout	Telmisartan 80 mg + Amlodipine 10 mg qd								
Sequence 2	Telmisartan 80 mg + Amlodipine 10 mg qd									15 days	Telmisartan alone 80 mg qd								

Study Drug

1. Telmisartan 80 mg tablets (Micardis[®], batch # 508965)
2. Amlodipine 10 mg tablets (Norvasc[®], batch # 510299030 D)

Pharmacokinetic Blood Sampling

Venous blood samples were collected at:

1. Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h post dose
2. Day 2- Day 8: pre-dose
3. Day 9: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 12, and 144 h post-dose

Assay Methods

Telmisartan: An ELISA method was used for the quantification of telmisartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.03 – 30 ng/mL with LLOQ of 0.3 ng/mL (%CV \leq 3.1, %RE: -3.2 – 3.7). The precision of the quality control samples was \leq 5.6% and the accuracy was -1.5% – 5.2%.

Amlodipine: A validated HPLC-MS/MS method was used for the quantification of amlodipine in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.05 – 10 ng/mL with LLOQ of 0.05 ng/mL (%CV \leq 9.89, %RE - 1.4 - 2.5). The precision of the quality control samples was \leq 5.7% and the accuracy was 2.3 – 3.1%.

Pharmacokinetics Data Analysis

Telmisartan and amlodipine PK parameters ($C_{\max,ss}$, $AUC_{0-24,ss}$, C_{\max} , T_{\max} , $AUC_{0-24,1}$, $C_{pre,N}$, $T_{\max,ss}$, $C_{min,ss}$, $t_{1/2,ss}$) were computed by standard non-compartmental method of analysis

Statistical Method

Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-24,ss}$ and $C_{\max,ss}$ and their two-sided 90% confidence intervals were calculated. The statistical model was ANOVA on the logarithmic scale, including effects for sequence, subjects within sequences, period and treatment. Confidence intervals were based on the residual error from ANOVA.

Results

Telmisartan:

Telmisartan Steady-state was achieved by Day 6 as shown in Figures 1 and 2. The inter-subject variability of telmisartan was high in the absence and presence of amlodipine. Amlodipine steady -state was achieved by Day 6 as shown in Figure 3.

The systemic exposure of telmisartan is not affected by the co-administration of amlodipine, as shown in the table below. It should be noted that lower bound of the 90% CI for C_{\max} is less than 0.8.

Parameter	N	Geometric Mean (% CV)		Reference (T alone)	Ratio T/R	90% CI	
		Test (T+A)	N			Lower	Upper
AUC _{0-24,ss} (ng h/mL)	36	998.7 (95.1)	36	1022.8 (74.0)	97.6	89.49	106.53
C _{max,ss} (ng/mL)	36	242.4 (118)	36	272.4 (105)	89.0	76.3	103.8

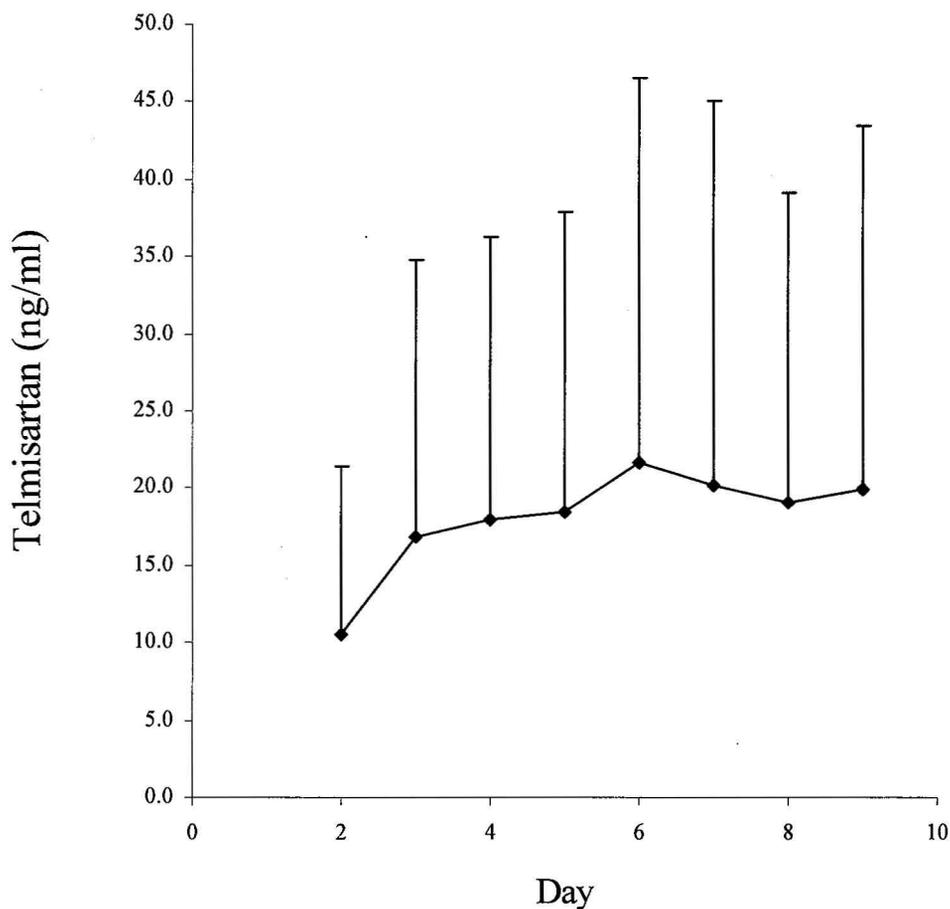


Figure 1. Telmisartan trough plasma concentration on Day 2- Day 9 following the administration of telmisartan alone. Each point represents the average and error bars represent the standard deviation.

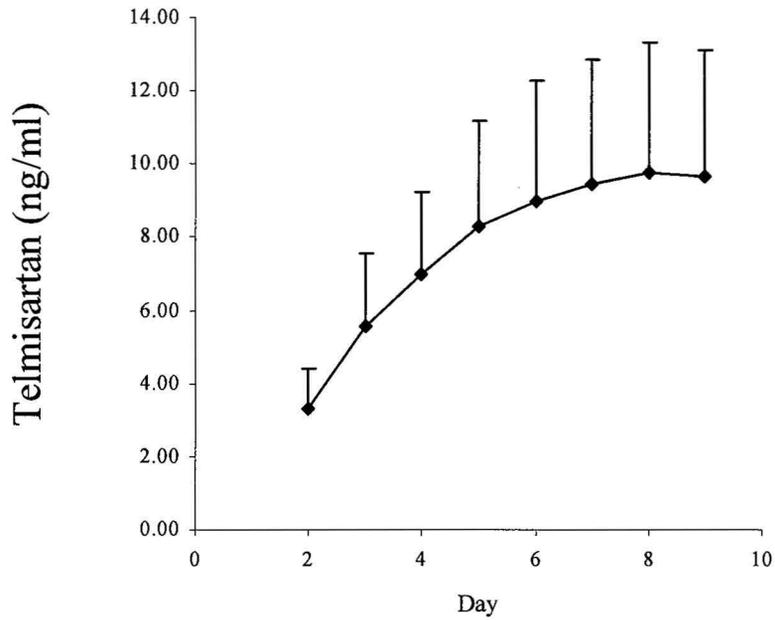


Figure 2. Telmisartan trough plasma concentration on Day 2 - Day 9 following the co-administration of telmisartan and amlodipine. Each point represents the average and error bars represent the standard deviation.

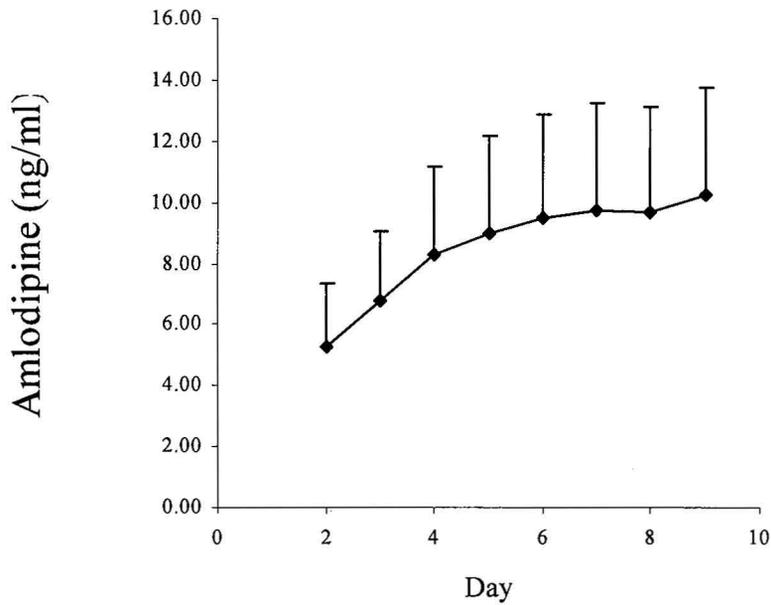


Figure 3. Amlodipine trough plasma concentration on Day 2 - Day 9 following the co-administration of telmisartan and amlodipine. Each point represents the average and error bars represent the standard deviation.

Safety

No death or any other serious adverse events occurred during this study. Headache was the most frequently reported adverse event, and was considered severe in one case.

Conclusion

Amlodipine at steady state does not alter the steady state systemic exposure of telmisartan.

Drug-Drug Interaction Study No. 502.126

Report #	502.126
Investigator	C.A.P.F.Su, M.D.
Study Site	Boehringer Ingelheim Deutschland GmbH, Human Pharmacology Center, Biberach, Germany.
Study Period	January 1995 – March 1995

Title

Pharmacokinetic of repeated oral doses of 10 mg amlodipine daily and of 10 mg amlodipine and 120 mg telmisartan (BIBR 227 SE) daily in cross-over randomized open study in healthy volunteers

Objectives

To assess the safety and pharmacokinetic interactions between amlodipine and telmisartan

Study Rationale

Telmisartan and amlodipine will be used in a fixed dose combination tablet, and the current study will evaluate the effect of telmisartan on the steady state pharmacokinetics of amlodipine.

Study Subjects

Twelve male subjects participated in the study with mean age of 34.7 ± 9.8 years. All subjects completed the study.

Study Design

This is an open-label, randomized, cross-over study in healthy volunteers. The study design is illustrated in the scheme below:

Day	1	2	3	4	5	6	7	8	9	Washout	1	2	3	4	5	6	7	8	9
sequence 1	Amlodipine alone 10 mg qd										Telmisartan 120 mg + Amlodipine 10 mg qd								
Sequence 2	Telmisartan 120 mg + Amlodipine 10 mg qd									13 - 15 days	Amlodipine alone 10 mg qd								

Study Drugs

1. Telmisartan 40 mg (batch # TA 030 3A1A) and 80 mg (batch # TA 030 2A1A) tablets
2. Amlodipine 5 mg tablets (Norvasc[®], batch # NA)

Pharmacokinetic Blood Sampling

Venous blood samples were collected at:

1. Day 1: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 h post dose
2. Day 2- Day 8: pre-dose
3. Day 9: pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 h post-dose

Assay Method

Telmisartan: An HPLC-fluoresce method was used for the quantification of telmisartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.5 – 50 ng/mL with LLOQ of 0.5 ng/mL (%CV \leq 4.6, %RE: -4.5 – 2.1). The precision of the quality control samples was \leq 4.3% and the accuracy was -2.4% – 0.8%.

Reviewer Note: The provided chromatograms have no scale and are not adequate.

Amlodipine: A GC-MS method was used for the quantification of amlodipine in plasma and urine.

During the analysis of the study unknown plasma samples, the calibration range was 0.1 – 20 ng/mL with LLOQ of 0.1 ng/mL (%CV \leq 7.2, %RE -8.5 – 7.1). The precision of the quality control samples was \leq 8.63% and the accuracy was -0.5 – 4.69%.

During the analysis of the study unknown urine samples, the calibration range was 50 – 1000 ng/mL with LLOQ of 50 ng/mL. The precision of the quality control samples was \leq 11.3% and the accuracy was -5.9 – 6.7%.

Pharmacokinetics Data Analysis

Telmisartan and amlodipine PK parameters ($C_{max,ss}$, $AUC_{0-24,ss}$, C_{max} , T_{max} , $AUC_{0-24,1}$, $C_{pre,N}$, $t_{max,ss}$, $C_{min,ss}$, $t_{1/2,ss}$) were computed by standard non-compartmental method of analysis

Statistical Method

All data were reported descriptively.

Results

Amlodipine and telmisartan steady-state was achieved by Day 6 as shown in Figures 1, 2, and 3. The systemic exposure of amlodipine is not affected by the co-administration of telmisartan, as shown in the table below:

Parameter	N	Geometric Mean (% CV)		Reference (A alone)	Ratio T/R	90% CI	
		Test (T+A)	N			Lower	Upper
AUC _{0-24,ss} (ng h/mL)	12	352 (30.9)	12	331 (32.1)	106	97.5	116
C _{max,ss} (ng/mL)	12	18.7 (29.6)	12	17.7 (29.6)	105.6	97.5	115

Reviewer Note: Since the sponsor indicated initially in the study report that there was no statistical plan, amlodipine systemic exposure (AUC_{0-24,ss}, C_{max,ss}) parameter generated by the sponsor were used to construct the 90% CI for the geometric mean of each parameter in the absence and presence of telmisartan using WinNonlin. The results obtained were identical to those reported by the sponsor.

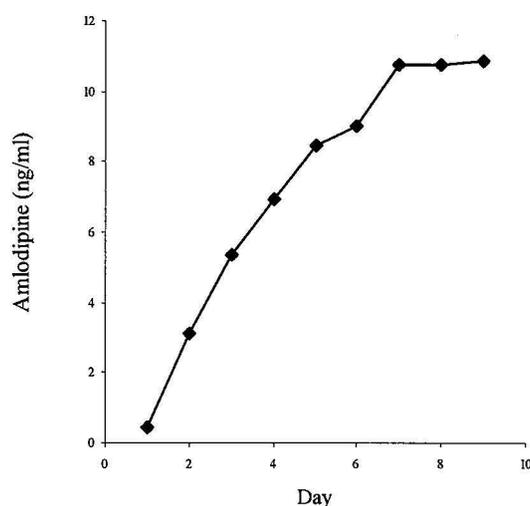


Figure 1. Amlodipine trough plasma concentration on Day 2- Day 9 following the administration of amlodipine alone. Each point represents the average.

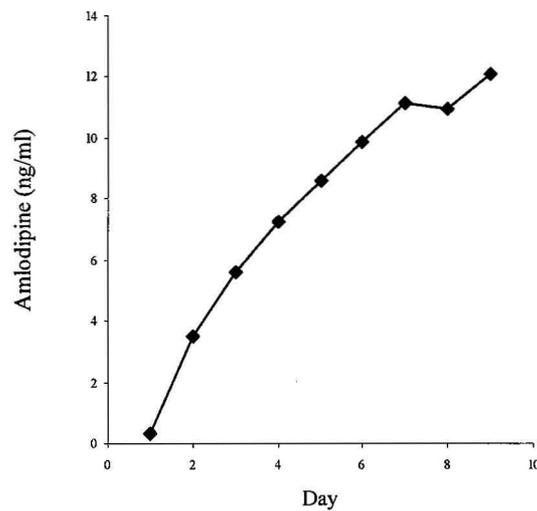


Figure 2. Amlodipine trough plasma concentration on Day 2 - Day 9 following the co-administration of telmisartan and amlodipine. Each point represents the average.

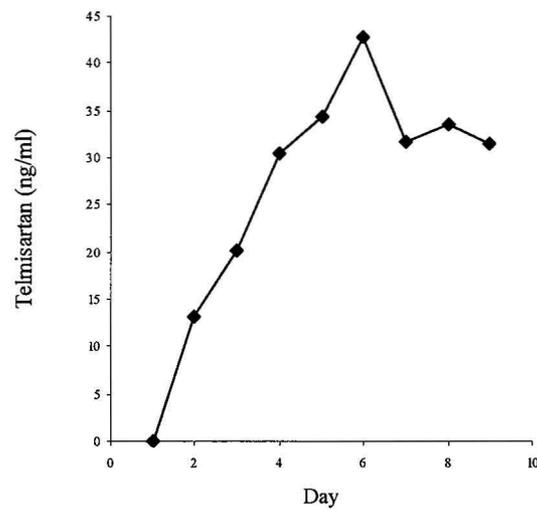


Figure 3. Amlodipine trough plasma concentration on Day 2 - Day 9 following the co-administration of telmisartan and amlodipine. Each point represents the average.

Safety

No death or any other serious adverse events occurred during this study. Headache was the most frequently reported adverse event, and was considered severe in one case.

Conclusion

Telmisartan at steady-state does not alter the steady-state systemic exposure of amlodipine.

Food Effect Study No. 1235.12

Report #	1235.12
Investigator	Sybille Baumann, M.D.
Study Site	(b) (4)
Study Period	09/20/2007-11/05/2007

Title

Influence of food on the bioavailability of 80 mg telmisartan/10 mg amlodipine fixed dose combination in healthy male and female volunteers. An open-label, randomized, single-dose, two period, crossover study.

Objective

To investigate the effect of food intake on the bioavailability of a fixed dose combination of 80 mg telmisartan/ 10 mg amlodipine following a high fat breakfast.

Study Rationale

Food reduces the bioavailability of telmisartan, but this does not alter the bioavailability of amlodipine. This study will evaluate the effect of food on the bioavailability and pharmacokinetics of the highest dose strength of the fixed dose combination to be marketed (80 mg telmisartan and 10 mg amlodipine).

Study Subjects

Thirty nine subjects (20 males and 20 females) participated in the study with mean age of 35.6 ± 10.1 years. Thirty nine subjects completed the study.

Study Design

This was an open-label, randomized, two-sequence, two-period crossover food effect study. No concomitant therapy was allowed except for oral contraceptives as well as ovary and thyroid hormone replacement.

Study Drug

Telmisartan (80mg) /amlodipine (10 mg), fixed dose combination tablet administered with 240 mL water.

For dose administration in the fasted state, subjects were required to fast from 10 hours prior to dosing.

For dose administration in the fed state, subjects received a FDA-defined high fat, high calorie breakfast prior to dosing. The meal was ingested over a 30-minute period and no further food was permitted until at least 4 hours post-dose. The table below shows the details of the provided meal:

Two eggs
Two strips of bacon
Butter
Two toast bread slices
Hash brown potatoes
240 mL whole milk
Total calorific content: 945 kcal
Total Kcal from fat content: 500-600 (53% - 64% of total calorific content)
Total Kcal from protein content: 150 g (16% of total calorific content)

Pharmacokinetic Blood Sampling

Venous blood samples were collected:

3. Telmisartan: At pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose.
4. Amlodipine: At pre-dose and at 0.5, 1, 2, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 post-dose.

Assay Method

Telmisartan: An ELISA method was used for the quantification of telmisartan in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.03 – 30 ng/mL with LLOQ of 0.3 ng/mL (%CV ≤ 3.0, %RE: -2.4 – 3.2). The precision of the quality control samples was ≤ 6.4% and the accuracy was -7.4% – 1.3%.

Amlodipine: A validated HPLC-MS/MS method was used for the quantification of amlodipine in plasma. During the analysis of the study unknown plasma samples, the calibration range was 0.05 – 10 ng/mL with LLOQ of 0.05 ng/mL (%CV ≤ 9.8, %RE: -3.0 – 5.0). The precision of the quality control samples was ≤ 2.6% and the accuracy was -4.9% – 0.2%.

Pharmacokinetics Data Analysis

Telmisartan and amlodipine primary PK parameters (C_{max} and $AUC_{0-\infty}$) were computed by standard non-compartmental methods of analysis

A mixed-effect analysis of variance (ANOVA) model was used to compare the pharmacokinetic parameters of amlodipine and telmisartan for each dietary condition (fed and fasted). Two-sided 90% confidence intervals (CIs) for the intra-subject fed-to-fasted

ratio (as estimated by the ratio of the geometric means) of each of $AUC_{0-\infty}$ and C_{max} were calculated.

Results

Food significantly reduces telmisartan $AUC_{0-\infty}$ and C_{max} by 24.3% and 60.1% respectively, as shown in the table below and Figure 1. Median T_{max} under fed conditions (2.0 h, range 0.5 -12.0) was higher than that observed under fast conditions (0.98 h, range 0.5 - 2.5).

Parameter	Geometric Mean (%CV)		Ratio Fed/Fast	90% CI	
	Fast	Fed		Lower	Upper
$AUC_{0-\infty}$ (ng h/mL)	1210 (82.9)	912 (72.9)	75.7	71.2	80.5
C_{max} (ng/mL)	192 (99.6)	77.2 (76.5)	39.9	33.1	48.1

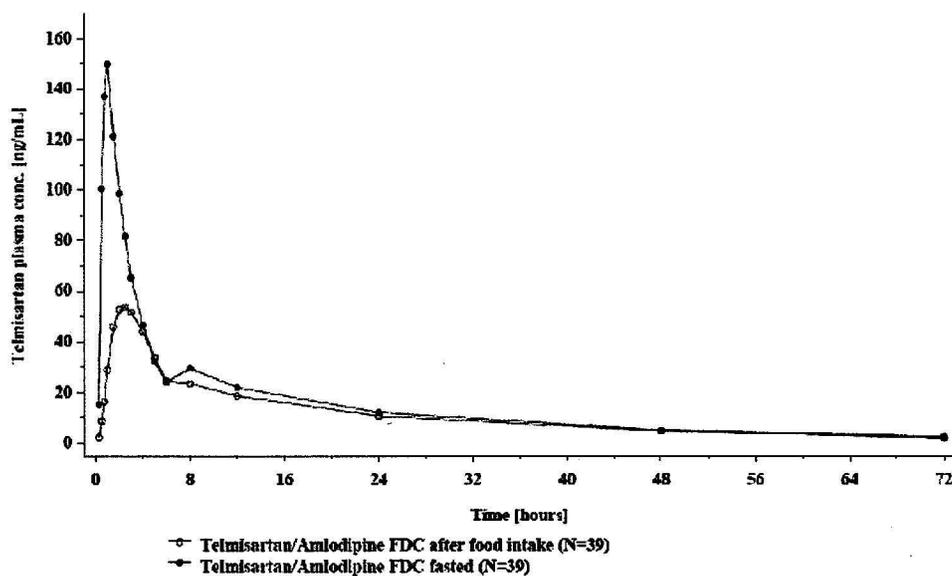


Figure 1. Telmisartan plasma concentration-time profile following the administration of a single oral dose of telmisartan (80 mg) and amlodipine (10 mg) fixed dose combination under fast and fed conditions.

Food does not affect the systemic exposure of amlodipine, as shown in the table below:

Parameter	Geometric Mean (%CV)		Ratio Fed/Fast	90% CI	
	Fast	Fed		Lower	Upper
AUC _{0-∞} (ng h/mL)	331 (32.5)	351 (30.2)	107.7	103.7	111.8
C _{max} (ng/mL)	6.54 (29.9)	6.77 (25.0)	104.3	100.3	108.5
T _{max} * (h)	6.0 (2.0-10.1)	5.08 (1.0-12.0)			

* Median and Range

Safety

No death or any other serious adverse events occurred during this study.

Conclusions

1. Food significantly reduces telmisartan AUC_{0-∞} by 24.3% and C_{max} 60.1%.
2. Food does not alter amlodipine AUC_{0-∞} and C_{max}.

Analytical Method Validation Review

Telmisartan

1. An ELISA method was used in studies # 1253.12, 1235.2, and 1235.3. The data provided below were obtained from the original validation report issued in October 5, 2000 (Report No. B1358). The ELISA method was modified five times since then, and the re-validation results from the last update (January 8, 2007) were reviewed and are acceptable.

Method		ELISA
Analyte		Telmisartan
Matrix		Plasma
Calibration Range		0.03 - 30.0 ng/mL 4-parameter logistic fit, variance weighing
LLQ (calculated)		0.03 ng/mL
Specificity		Blank plasma did not show any unspecific matrix effect above LLQ.
Precision % CV	Intra-day	≤ 5.9
	Inter-day	≤ 4.4
Accuracy % RE	Intra-day	2.1 – 5.0
	Inter-day	-2.0 – -1.4
% Recovery		102 - 105
Stability	RT	> 1 day
	4 °C	> 1 day
	-20 °C	> 1 year
	Freeze-Thaw	> 3 cycles

2. An HPLC-Fluorescence analytical method was used in study 1235.4.

Method		HPLC-Fluorescence
Analyte		Telmisartan
Matrix		Plasma
Calibration Range		0.5 - 400.0 ng/mL
LLQ (calculated)		0.5 ng/mL
Specificity		Analysis of blank and spiked plasma confirms method selectivity for the three analytes. Chromatograms were provided
Precision % CV	Intra-day	≤ 1.5
	Inter-day	≤ 2.7
Accuracy % RE	Intra-day	-0.9 – 2.7
	Inter-day	-2.2 – 3.4
% Recovery		89.4 – 94.2
Stability	RT	> 1 day
	4 °C	NA
	-20 °C	> 351 days
	Freeze-Thaw	> 3 cycles

Amlodipine

An HPLC-MS/MS analytical method was used in studies 1235.12, 1235.2, 1235.3, and 1235.4 (Report No. PK0618V). Note that this summary was obtained from the revalidation report which was performed to increase the linear range for the upper limit from 5 ng/mL to 10 ng/mL. Recovery, room temperature and freeze-thaw stability data are obtained from the original method validation report and were not re-evaluated in the updated procedure.

Method		HPLC-MS/MS
Analyte		Amlodipine
Matrix		Plasma
Calibration Range		0.05 - 10.0 ng/mL
LLQ (calculated)		0.05 ng/mL
Specificity		Analysis of blank and spiked plasma confirms method selectivity for the three analytes. Chromatograms were provided
Precision % CV	Intra-day	≤ 4.3
	Inter-day	≤ 5.0
Accuracy % RE	Intra-day	-1.0 – 0.6
	Inter-day	-0.9 – -1.3
% Recovery		42.4 -44.0
Stability	RT	> 24 hours
	4 °C	NA
	-20 °C	> 3 month
	Freeze-Thaw	> 4 cycles

Reviewer Note: The validation of the above methods is acceptable.

4.3 OCP Filing Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information			Information
NDA Number	22-401	Brand Name		Twynsta® (proposed)
OCPB Division (I, II, III)	I	Generic Name		Telmisartan/ Amlodipine
Medical Division	Cardio-Renal	Drug Class		ACE II inhibitor/ Ca Channel Blocker
OCPB Reviewer	Islam Younis	Indication(s)		Hypertension
OCPB Team Leader	Elena Mishina	Dosage Form		Tablet
		Dosing Regimen		T(mg)/A(mg): 40/5, 40/10, 80/5, 80/10
Date of Submission	12/18/2008	Route of Administration		Oral
Estimated Due Date of OCPB Review	10/18/2009	Sponsor		Boehringer Ingelheim
PDUFA Due Date	12/18/2009	Priority Classification		Standard
Division Due Date	10			
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				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	3	3	
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:	X	1	1	
In-vivo effects of primary drug:	X	1	1	
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	2	2	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution: (IVIVC):				
Bio-wavier request based on BCS BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	█	8	8	
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Islam R. Younis, 05/05/2009			
Secondary reviewer Signature and Date	Angelica. Dorantes, 05/05/2009			

CC: NDA 22-401, HFD-110(NguyenQ), HFD-860(DorantesA, UppoorR, MethaM,)

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

/s/

Islam R Younis
5/8/2009 07:15:13 AM
PHARMACIST

Angelica Dorantes
5/8/2009 03:23:18 PM
BIOPHARMACEUTICS