

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-314

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

Office of Clinical Pharmacology Review

NDA number: 22-314

Submission type: Original, N-000

Submission date: 06/30/2008

Applicant name: Novartis Pharmaceuticals Corporation

Proposed brand name: Exforge HCT

Generic name: Valsartan / Hydrochlorothiazide / Amlodipine (V/H/A)

Dosage form: Tablet

Dosage strengths (V/H/A in mg): 320/25/10, 160/25/10, 160/25/5, 160/12.5/10, 160/12.5/5

Proposed indication: Treatment of — hypertension **b(4)**

OCP division: DCP1

OND division: Cardiovascular and renal products

Primary reviewer: Divya Menon-Andersen, PhD

Secondary reviewer / Team leader: Angelica Dorantes, PhD

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1 EXECUTIVE SUMMARY

Novartis Pharmaceuticals Corporation is seeking approval via the 505(b) 2 pathway of Exforge HCT, a fixed dose combination (FDC) tablet of valsartan / hydrochlorothiazide / amlodipine (V/H/A) for use in the treatment of _____ hypertension. Exforge HCT will be marketed in five strengths for once daily administration.

b(4)

The application contains six clinical studies in support of the sponsor's claims of efficacy and safety. These included three bioequivalence/relative bioavailability studies (study numbers VEA489A2305, VEA489A2305, VEA489A2105), one food effect study (study number VEA489A2310), one drug interaction study conducted in hypertensive subjects (study number VEA489A2104), and an active controlled efficacy trial conducted in 2200 hypertensive subjects (study number VEA489A2302).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 22-314.

Clinical Pharmacology: The results of the bioequivalence studies submitted in the application established an adequate link between the results of the pivotal efficacy trial conducted with the free combination, and the final market image tablet (to-be-marketed formulation). Further, it was shown that there was no clinically significant pharmacokinetic drug interaction between the components of the FDC, and that food did not affect the pharmacokinetics of Exforge HCT.

Labeling: The clinical pharmacology information included in the proposed labeling is acceptable.

BE Audit Report: The DSI reports for the audits for the analytical and clinical sites of bioequivalence studies VEA489A2305 and VEA489A2305 will be submitted in April 2009. OCP will review the reports once submitted, and OCP's recommendations will be documented as an amendment to this current OCP review.

The NDA is considered acceptable from a clinical pharmacology perspective.

1.2 Phase 4 Requirements / Commitments

Not applicable (there are no Phase 4 requirements or commitments).

Divya Menon-Andersen, PhD
Reviewer, Division of Clinical Pharmacology 1

Date: February 27, 2009

Angelica Dorantes, PhD
Secondary reviewer / Team leader (Acting), Cardiovascular & Renal Products
Division of Clinical Pharmacology 1

Clinical Pharmacology Briefing:

An optional intra - division level briefing was held on February 26, 2009; and attended by Jean Fourie, Akansha Khandelwal, Sarah Schreiber, Pravin Jadhav, Ramana Uppoor, Islam Younis, Angelica Dorantes and Divya Menon-Andersen.

Cc: DorantesA, UppoorR, MehulM

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Exforge HCT is a FDC tablet of V/H/A for use in the treatment of hypertension. All three components of Exforge HCT are approved for use in hypertension, and pharmacokinetics (PK) and pharmacodynamics (PD) are well characterized.

The Clinical Pharmacology and Biopharmaceutics program for Exforge HCT was designed primarily to bridge the clinical efficacy and safety data obtained with the free combination to the to-be-marketed formulation. Exforge HCT will be formulated in five strengths of V/H/A that span the approved dosing range of the individual components for oral administration. These are 320/25/10 mg, 160/25/10 mg, 160/25/5 mg, 160/12.5/10 mg, and 160/12.5/5 mg. All studies were reviewed.

1.3.1 Bioequivalence

Two definitive bioequivalence studies were conducted to determine the bioavailability of the 160/25/10 and 160/12.5/5 mg strengths, relative to the free combination (study numbers VEA489A2305, VEA489A2305). A biowaiver, based on proportionality and compositional similarity, was requested for the remaining three strengths (320/25/10, 160/25/5, 160/12.5/10 - reviewed by ONDQA). A third study was conducted to determine the bioavailability of the over-encapsulated amlodipine, used in the pivotal clinical trial, relative to Norvasc (study number VEA489A2105).

Following administration of a single dose of Exforge HCT in healthy volunteers, peak plasma levels of V, H, and A were attained approximately at 3h (range: 1 to 4 h), 2h (range: 1 to 4), and between 6 to 8 h (range: 6 to 16h), respectively. Across studies, the mean elimination half-life for V/H/A was estimated to be about 14 to 18h, 9 to 11h, and 40 to 45h, respectively.

The rate and extent of absorption of V, H, and A following administration of a single dose of prototype I of Exforge HCT (160/25/10 and 160/12.5/5 mg) were equivalent to that observed following administration of a single dose of the free combination. **Table 1** presents the results of the bioequivalence studies for Exforge HCT

Table 1: Relative bioavailabilities of V/H/A following administration of a single dose of Exforge HCT (Ref: Study VEA489A2305 and 2306, Tables 14.2-1.1 to 14.2-1.6)

Valsartan

	VEA489A2305 (160/12.5/5 mg)			VEA489A2306 (160/25/10 mg)		
	Geometric mean		Ratio (90% CI for ratio)	Geometric mean		Ratio (90% CI of ratio)
	Prot I	Ref		Prot I	Ref	
AUC _{0-∞}	24369.5	23476.7	1.04 (0.90, 1.20)	30325.3	31735.9	0.96 (0.86, 1.06)
AUC _{0-τ}	23926.4	23355.4	1.02 (0.88, 1.19)	31228.9	31645.0	0.99 (0.89, 1.10)
C _{max}	3191.0	3181.3	1.00 (0.84, 1.20)	4657.2	4793.7	0.97 (0.85, 1.11)

Hydrochlorothiazide

	VEA489A2305 (160/12.5/5 mg)			VEA489A2306 (160/25/10 mg)		
	Geometric mean		Ratio (90% CI for ratio)	Geometric mean		Ratio (90% CI of ratio)
	Prot I	Ref		Prot I	Ref	
AUC _{0-∞}	498.8	503.2	0.99 (0.95, 1.04)	985.7	979.9	1.01 (0.96, 1.06)
AUC _{0-τ}	477.1	480.9	0.99 (0.94, 1.04)	1016.5	1013.3	1.00 (0.96, 1.05)
C _{max}	72.7	72.5	1.00 (0.91, 1.10)	145.4	149.7	0.97 (0.89, 1.06)

Amlodipine

	VEA489A2305 (160/12.5/5 mg)			VEA489A2306 (160/25/10 mg)		
	Geometric mean		Ratio (90% CI for ratio)	Geometric mean		Ratio (90% CI of ratio)
	Prot I	Ref		Prot I	Ref	
AUC _{0-∞}	137.0	136.2	1.01 (0.94, 1.08)	284.4	278.1	1.02 (0.94, 1.11)
AUC _{0-τ}	125.8	125.5	1.00 (0.94, 1.07)	303.8	298.6	1.02 (0.93, 1.11)
C _{max}	2.7	2.6	1.03 (0.96, 1.11)	5.4	5.3	1.02 (0.94, 1.11)

For both the strengths of Exforge HCT tested, prototype I was selected as the to-be-marketed formulation.

1.3.2 Food Effect

The effect of food on the disposition of V/H/A following administration of a single dose of Exforge HCT was evaluated in study VEA489A2310, in healthy volunteers. Food does not affect the PK of Exforge HCT. The results of the food effect study are presented in Table 2.

Table 2: Statistical analysis of log-transformed AUC and C_{max} of Exforge HCT 320/25/10 mg fed (Test) and Exforge HCT 320/25/10 mg fasted (Reference) (Ref: Table 14.2-1.2)

Valsartan

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % confidence interval	
	Test (Fed)	Ref (Fasted)		Lower	Upper
AUC _{0-∞}	47222.27	41345.42	1.14	0.99	1.31
AUC _{0-τ}	46660.46	40904.29	1.14	0.99	1.31
C _{max}	5338.09	4738.44	1.12	0.98	1.29

Hydrochlorothiazide

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % confidence interval	
	Test (Fed)	Ref (Fasted)		Lower	Upper
AUC _{0-∞}	1067.29	980.84	1.09	1.02	1.16
AUC _{0-τ}	1033.80	941.12	1.1	1.02	1.18
C _{max}	110.79	129.66	0.86	0.79	0.93

Amlodipine

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % confidence interval	
	Test (Fed)	Ref (Fasted)		Lower	Upper
AUC _{0-∞}	225.16	209.81	1.09	1.04	1.15
AUC _{0-τ}	206.29	195.80	1.09	1.03	1.15
C _{max}	4.61	4.23	1.11	1.05	1.18

1.3.3 Drug Interaction

The potential for a PK drug interaction between V/H/A on chronic administration of Exforge HCT was assessed in hypertensive patients (study VEA489A2104). **Figure 1** presents a graphical comparison of the distribution of the observed AUC and C_{max} for the individual components of the dual (V/A, V/H, and H/A) and triple combination (V/H/A). As seen in the figure, the range of AUC and C_{max} attained at steady state are similar. However, the 90% confidence intervals for AUC and C_{max} are not within the pre-determined no effect boundaries and are therefore statistically significant. Specifically, at steady state, the mean AUC and C_{max} of valsartan increased by 25 and 22%, respectively (**Figure 1**). However, given the observed inter-subject variability in valsartan PK (~ 50% CV), the increased AUC and C_{max} observed in this study is judged not to be of any clinical significance.

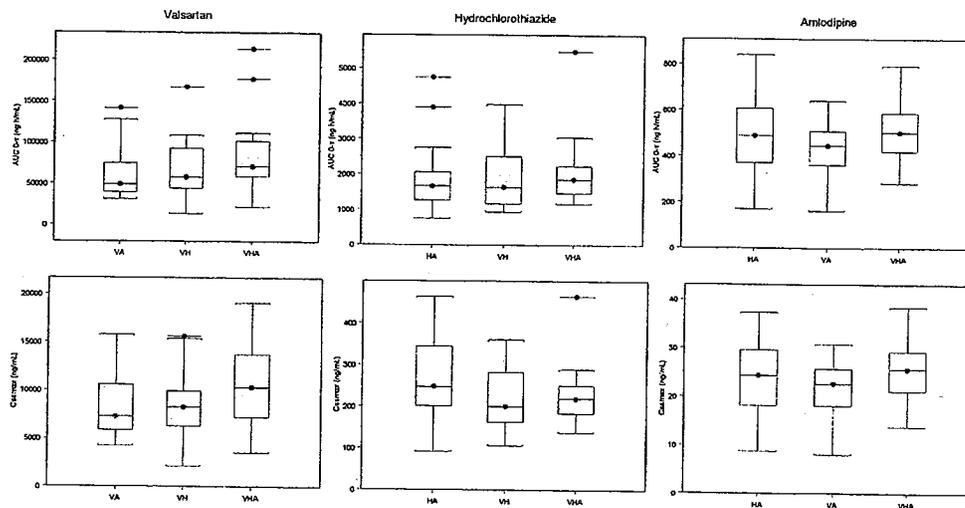


Figure 1: Reviewer generated plots of AUC (top panel) and C_{max} (bottom panel) distribution for V/H/A 320/25/10 mg following once daily administration of Exforge HCT to steady state.

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2 QUESTION BASED REVIEW

This is an abridged version of the question based review.

2.1 General Attributes of the Drugs and Drug Product

Exforge HCT is a film coated fixed dose combination tablet of **valsartan**, **hydrochlorothiazide** and **amlodipine**. All three components of Exforge HCT have been previously approved for marketing in the US, for use in the treatment of hypertension.

DRUGS:

Valsartan (V), an angiotensin receptor blocker, is approved for use in the treatment of hypertension in adults over the dose range of 80 to 320 mg, given once daily. Peak plasma concentrations are attained within two to four hours after dosing. Absolute bioavailability for valsartan (Diovan) is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%.

Hydrochlorothiazide (H), a diuretic, is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours. Thiazide diuretics are eliminated by the kidney, with a terminal half-life of 5-15 hours.

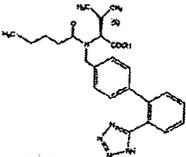
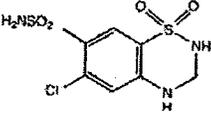
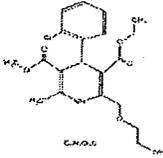
Amlodipine (A) is a long acting calcium channel blocker. After oral administration of therapeutic doses of amlodipine besylate tablets, peak plasma concentrations are attained between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours.

DRUG PRODUCT:

Exforge HCT: Following administration of a single dose of **Exforge HCT** in healthy volunteers, peak plasma levels of V, H, and A were attained approximately at 3h (range: 1 to 4 h), 2h (range: 1 to 4), and between 6 to 8 h (range: 6 to 16h), respectively. Across studies, the mean elimination half-life for V/H/A was estimated to be about 14 to 18h, 9 to 11h, and 40 to 45h, respectively.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Exforge HCT is a fixed dose combination tablet of valsartan, hydrochlorothiazide and amlodipine.

	Valsartan	Hydrochlorothiazide	Amlodipine
Description	White microcrystalline powder bitter to taste	white crystalline powder	white to pale yellow crystalline powder
Chemical name	N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide	3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate
Molecular formula	C ₂₄ H ₂₉ N ₅ O ₃	C ₇ H ₈ ClN ₃ O ₄ S ₂	C ₂₆ H ₂₅ ClN ₂ O ₅ •C ₆ H ₆ O ₃ S
Molecular weight	435.5	297.73	567.1
Structural formula			
Solubility	soluble in ethanol and methanol and slightly soluble in water	slightly soluble in water, freely soluble in sodium hydroxide solution, sparingly soluble in methanol	Slightly soluble in water and sparingly soluble in ethanol.

Formulation: In addition to the active ingredients listed in the table above, Exforge HCT contains the following inactive excipients: microcrystalline cellulose, crospovidone, _____, and magnesium stearate. _____ hypromellose, titanium dioxide, polyethylene glycol 4000, talc, iron oxide red, and iron oxide yellow.

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2.1.2 What are the proposed dosages and routes of administration?

Exforge HCT will be formulated in five strengths of V/H/A that span the approved dosing range of the individual components for oral administration. These are 320/25/10 mg, 160/25/10 mg, 160/25/5 mg, 160/12.5/10 mg, and 160/12.5/5 mg.

The approved dosing range for V, H, and A in hypertension are 80 to 320 mg, 5 to 50 mg, and 2.5 to 10 mg, respectively.

2.1.3 What are the proposed mechanisms of action and therapeutic indications?

Exforge HCT is indicated in the treatment of _____ hypertension. The mechanisms of action of the individual components of Exforge HCT are state below.

b(4)

Valsartan is an angiotensin receptor blocker. It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. It is approved for use in the treatment of (1) hypertension in adults and children above six years (2) heart failure and (3) post myocardial infarction.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The mechanism of antihypertensive effect of thiazides is unknown. Hydrochlorothiazide is approved for use in the treatment of hypertension.

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. 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. Amlodipine is approved for the treatment of (1) hypertension in adults and children above six years (2) angina and (3) coronary artery disease.

2.2 General Clinical Pharmacology

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

Six clinical studies (five clinical pharmacology + one efficacy) were conducted with Exforge HCT to support proposed dosing and claims. All the clinical pharmacology studies were reviewed and the individual study reports are presented in section 4.2. A summary of all six studies submitted in this application is provided in Table 3.

Table 3: Key design features of the clinical studies conducted with Exforge HCT.

Study number	Design	Study population	Treatments	End-point
VEA489A2305 Relative BA/BE 160/12.5/5 mg	Single center, open-label, four period, crossover design	Healthy volunteers	Single dose of FDC, prototype I, FDC, prototype II, FDC, prototype II, and Free combination	PK
VEA489A2306 Relative BA/BE 160/25/10 mg	Single center, open-label, three period, crossover design	Healthy volunteers	Single dose of FDC, prototype I, FDC, prototype II, Free combination	PK
VEA489A23 Relative BA	Single center, open-label, two period, crossover design	Healthy volunteers	Single dose of over encapsulated amlodipine 5 mg, Norvasc 5 mg	PK
VEA489A2310 Food effect	Single center, two period, crossover design	Healthy volunteers	Single dose of 320/25/10 mg FMI tablet fed and fasted	PK
VEA489A2304 Drug Interaction	Multi-center, open-label, parallel design	Hypertensive patients	V/H: 320 / 25 mg V/A: 320 / 10 mg H/A: 25 / 10 mg V/H/A: 320 / 25 / 10 mg	PK
VEA489A2302 Efficacy	Multi-center, double-blind, parallel design	Hypertensive patients	V/H: 320 / 25 mg V/A: 320 / 10 mg H/A: 25 / 10 mg V/H/A: 320 / 25 / 10 mg	Blood pressure

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

Yes. V, H, and A are the only active moieties in Exforge HCT. Please refer to section 2.6 for details of the bioanalytical method.

2.2.3 Exposure-Response

2.2.3.1 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

Yes. Exforge HCT is a FDC of valsartan, hydrochlorothiazide, and amlodipine. The approved dosing range for valsartan, hydrochlorothiazide, and amlodipine in hypertension are 80 to 320 mg, 5 to 50 mg, and 2.5 to 10 mg, respectively. Exforge HCT will be formulated in five strengths of V/H/A that span the approved dosing range of the individual components for oral administration. These are 320/25/10 mg, 160/25/10 mg, 160/25/5 mg, 160/12.5/10 mg, and 160/12.5/5 mg.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters?

Please refer to section 2.1.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of intrinsic factors on exposure or response was not evaluated.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1.1 Drug Interaction

A drug interaction study was conducted to assess the potential for a PK drug interaction between V, H, and A when administered together as a triple combination. Plasma AUC and C_{max} of the individual components following administration of the triple combination were compared to that following administration of the corresponding dual combination. Tables 4(a) - (c) present the results of the statistical analysis of the drug interaction study.

Table 4(a): Summary of the statistical analysis for HCT and amlodipine.

		Adjusted geometric mean		Geometric mean ratio ³	90% CI for ratio ³
		V / H / A ¹ N = 23	H / A ² N = 23		
HCTZ	AUC _{0-t} (ng.h/mL)	1868.6	1726.1	1.08	0.89 - 1.32
	C _{ssmax} (ng/mL)	219.3	264.7	0.83	0.69 - 0.99
Amlodipine	AUC _{0-t} (ng.h/mL)	494.8	453.6	1.09	0.90 - 1.32
	C _{ssmax} (ng/mL)	25.1	22.8	1.10	0.92 - 1.32

Table 4(b): Summary of the statistical analysis for amlodipine and valsartan.

		Adjusted geometric mean		Geometric mean ratio ³	90% CI for ratio ³
		V / H / A ¹ N = 23	V / A ² N = 23		
Valsartan	AUC _{0-t} (ng.h/mL)	73385.6	58628	1.25	0.98 - 1.59
	C _{ssmax} (ng/mL)	9926.6	8136.3	1.22	0.98 - 1.52
Amlodipine	AUC _{0-t} (ng.h/mL)	494.8	451	1.10	0.91 - 1.33
	C _{ssmax} (ng/mL)	25.1	22.8	1.10	0.92 - 1.32

Table 4(c): Summary of the statistical analysis for valsartan and HCT.

		Adjusted geometric mean		Geometric mean ratio ³	90% CI for ratio ³
		V/H/A ¹ N = 23	V/H ² N = 25		
Valsartan	AUC _{0-t} (ng.h/mL)	73385.6	66902.5	1.10	0.88 - 1.37
	C _{ssmax} (ng/mL)	9926.6	8595.5	1.15	0.94 - 1.41
HCTZ	AUC _{0-t} (ng.h/mL)	1868.6	1813.3	1.03	0.86 - 1.24
	C _{ssmax} (ng/mL)	219.3	215.7	1.02	0.86 - 1.20

As seen in **Tables 4(a) to (c)**, at steady state, the mean AUC and C_{max} of valsartan increased by 25 and 22%, respectively. According to the current valsartan label, a two fold increase in plasma valsartan concentration (observed in hepatically impaired patients taking valsartan) does not warrant a dose adjustment. Also, given the observed inter-subject variability in valsartan PK (~ 50% CV), the increased AUC and C_{max} observed in this study is judged not to be of any clinical significance.

2.4.1.2 Food effect

Influence of food on systemic exposure to V, H, and A following administration of a single oral dose of Exforge HCT (320/25/10 mg) was evaluated in study VEA489A2310. **Table 5** presents the results of the statistical analysis of the food effect study. A small increase in the AUC and C_{max} of valsartan was observed in the fed state. For the reasons cited in section 2.4.1.1, this was judged not to be of any clinical significance.

Table 5: Summary of results of the statistical analysis of PK measures (Ref: study VEA489A2310, Tables 14.2-2.1 to 14.2-2.3).

	Geometric mean		Geometric mean ratio	
	Fed (n=35)	Fasting (n=35)	Estimate	90% CI
Valsartan				
C _{max} (ng/mL)	5327.61	4739.52	1.12	0.98 - 1.29
AUC _{0-t} (hr*ng/mL)	46645.61	40982.76	1.14	0.99 - 1.31
AUC _{0-x} (hr*ng/mL)	47199.80	41429.90	1.14	0.99 - 1.31
Hydrochlorothiazide				
C _{max} (ng/mL)	110.72	128.60	0.86	0.79 - 0.93
AUC _{0-t} (hr*ng/mL)	1031.83	940.63	1.10	1.02 - 1.18
AUC _{0-x} (hr*ng/mL)	1064.98	980.53	1.09	1.02 - 1.16
Amlodipine				
C _{max} (ng/mL)	4.64	4.18	1.11	1.05 - 1.18
AUC _{0-t} (hr*ng/mL)	208.65	191.96	1.09	1.03 - 1.15
AUC _{0-x} (hr*ng/mL)	228.31	208.89	1.09	1.04 - 1.15

2.5 General Biopharmaceutics

2.5.1 Was an adequate link established between the clinical service formulation and the to-be-marketed formulations?

Yes. Exforge HCT will be formulated in five strengths of V/H/A that span the approved dosing range of the individual components for oral administration. These are 320/25/10 mg, 160/25/10 mg, 160/25/5 mg, 160/12.5/10 mg, and 160/12.5/5 mg. Two definitive bioequivalence studies (160/12.5/5 and 160/25/10 mg strengths) were conducted to bridge the results of the pivotal efficacy trial to the to-be marketed formulation. **Tables 6(a) and (b)** present the results of the statistical analysis of the PK measures. A biowaiver, based on proportionality and compositional similarity, was requested for the remaining three strengths (320/25/10, 160/25/5, 160/12.5/10 - to be reviewed by ONDQA)

Table 6(a): Summary of results of the statistical analysis of PK measures for Exforge HCT 160/12.5/5 mg (Ref: study VEA489A2305, Tables 14.2-1.1 to 14.2-1.6).

Analyte	PK parameter	Ratio of geometric means (90% CI)		
		VEA489A Prototype I	VEA489A Prototype II	VEA489A Prototype III
Valsartan	AUC _(0-t)	1.02 (0.88-1.19)	1.13 (0.97-1.32)	1.10 (0.95-1.28)
	AUC _(0-inf)	1.04 (0.90-1.20)	1.15 (0.99-1.33)	1.19 (1.03-1.39)
	C _{max}	1.00 (0.84-1.20)	1.17 (0.97-1.40)	0.99 (0.83-1.18)
HCTZ	AUC _(0-t)	0.99 (0.94-1.04)	1.06 (1.00-1.11)	1.00 (0.95-1.05)
	AUC _(0-inf)	0.99 (0.95-1.04)	1.05 (1.00-1.10)	1.00 (0.95-1.05)
	C _{max}	1.00 (0.91-1.10)	1.08 (0.99-1.19)	0.99 (0.90-1.09)
Amlodipine	AUC _(0-t)	1.00 (0.94-1.07)	0.97 (0.90-1.04)	1.05 (0.98-1.13)
	AUC _(0-inf)	1.01 (0.94-1.08)	0.97 (0.91-1.04)	1.05 (0.98-1.13)
	C _{max}	1.03 (0.96-1.11)	0.99 (0.92-1.07)	1.06 (0.98-1.14)

Table 6(b): Summary of results of the statistical analysis of PK measures for Exforge HCT 160/25/10 mg (Ref: study VEA489A 2306, Tables 14.2-1.1 to 14.2-1.6).

Analyte	PK parameter	Ratio of geometric means (90% CI)	
		Prototype I	Prototype II
Valsartan	AUC _(0-t) (µg·h/mL)	0.96 (0.86, 1.06)	1.05 (0.94, 1.16)
	AUC _(0-∞) (µg·h/mL)	0.99 (0.89, 1.10)	1.07 (0.96, 1.19)
	C _{max} (µg/mL)	0.97 (0.85, 1.11)	1.03 (0.91, 1.17)
HCTZ	AUC _(0-t) (ng·h/mL)	1.01 (0.96, 1.06)	1.04 (0.99, 1.09)
	AUC _(0-∞) (ng·h/mL)	1.00 (0.96, 1.05)	1.03 (0.98, 1.08)
	C _{max} (ng/mL)	0.97 (0.89, 1.06)	1.01 (0.93, 1.10)
Amlodipine	AUC _(0-t) (ng·h/mL)	1.02 (0.94, 1.11)	1.06 (0.97, 1.15)
	AUC _(0-∞) (ng·h/mL)	1.02 (0.93, 1.11)	1.05 (0.97, 1.14)
	C _{max} (ng/mL)	1.02 (0.94, 1.11)	1.04 (0.96, 1.13)

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

Food has no clinically significant effect on the bioavailability of V, H, and A following administration of a single dose of Exforge HCT. Please refer to **Table 2** in section 1.3.2. of this document.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

Plasma concentrations of valsartan, hydrochlorothiazide, and amlodipine were simultaneously determined using a validated HPLC/MS/MS method.

2.6.2 For all moieties measured, is free, bound, or total measured?

Total concentrations of valsartan, hydrochlorothiazide, and amlodipine were measured.

2.6.3 What bioanalytical methods are used to assess concentrations?

Table 7 provides the details of the bioanalytical method used to support the PK studies. The method satisfied all criteria for ‘method validation’ and ‘application to routine analysis’ set by the ‘*Guidance for Industry: Bioanalytical Method Development*’, and was therefore acceptable. The same assay was used in all PK studies.

Table 7: Assay validation results for valsartan, hydrochlorothiazide, and amlodipine (Ref: Study Report DMPK – R0500857).

	Valsartan	Hydrochlorothiazide	Amlodipine
Standard curve range	5 to 5000 ng/mL (weighted $1/x^2$, $r = 0.9954$)	1 to 200 ng/mL (weighted $1/x^2$, $r = 0.9974$)	0.025 to 10 ng/mL (weighted $1/x^2$, $r = 0.9966$)
QC sample concentrations	5, 15, 500, 4000 ng/mL	1, 3, 40, 160 ng/mL	0.025, 0.075, 0.75, 8.0 ng/mL
Precision (%CV)	Intra-day: 1.8 to 2.3% At LLOQ: 6.1% Inter-day: 2.6 to 5.4% At LLOQ: 4.6%	Intra-day: 1.6 to 2.0% At LLOQ: 3.8% Inter-day: 2.6 to 3.8% At LLOQ: 6.3%	Intra-day: 1.5 to 5.9% At LLOQ: 6.6% Inter-day: 5.4 to 8.2% At LLOQ: 12.0%
Accuracy (Bias)	Intra-day: -14.4 to 2.0% At LLOQ: -10.6% Inter-day: -9.3 to 0.0% At LLOQ: -12.6%	Intra-day: -8.1 to 6.5% At LLOQ: -2.2% Inter-day: -6.3 to 8.8% At LLOQ: -1.9%	Intra-day: -11.7 to 6.0% At LLOQ: 8.4% Inter-day: -4.8 to 1.2% At LLOQ: -0.4%
Internal standard	D9 – valsartan Lot number: E-32438-135-45	$^{15}\text{N}_2$ - hydrochlorothiazide Lot number: KZ0545	D ₄ – amlodipine Lot numbers: E-7111056-45, E-34423-28-22
Reference standard	Valsartan Lot numbers: 6BAA9 Purity: 98.7%	Hydrochlorothiazide Lot numbers: 041K1522, 105K1758 Purity: > 99%	Amlodipine Lot numbers: A65012A, 0484001 Purity: 100%
Specificity	No interference	No interference	No interference
Recovery	Valsartan: 89 % D9 – valsartan: 87%	Hydrochlorothiazide: 49% D ₂ $^{15}\text{N}_2$ – hydrochlorothiazide: 50%	Amlodipine: 117% D ₄ – amlodipine: 112%
Matrix	Li heparinated human plasma	Li heparinated human plasma	Li heparinated human plasma
Stability (in human plasma)	Benchmark: 24 hours Freeze-thaw: 3 FT cycles Long term: 13 months at -18°C	Benchmark: 24 hours Freeze-thaw: 3 FT cycles Long term: 6 months at -18°C	Benchmark: 24 hours Freeze-thaw: 3 FT cycles Long term: 4 months at -18°C

3 PROPOSED LABELING

The proposed labeling for Exforge HCT is described in the following pages (1 to 30).

Labeling Comment:

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for Exforge HCT, and finds it acceptable.

30 Page(s) Withheld

 Trade Secret / Confidential (b4)

 x Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4 INDIVIDUAL STUDY REVIEWS

4.1.1 Study VEA489A2305 (Bioequivalence – 160/12.5/5 mg)

An open-label, randomized, single dose, four period, crossover design study to determine the relative bioavailability of three prototype 160/12.5/5 mg fixed combination valsartan/HCTZ/amlodipine tablets to a free combination of phase III-clinical service forms (CSFs) of 160 mg valsartan, 12.5 mg HCTZ, and 5 mg amlodipine.

Protocol number: CVEA489A2305

Investigator: _____ b(4)

Study site: _____

Study dates: 04/21/2006 to 06/09/2006

4.1.1.1 Objectives

The objectives of the study were to determine the bioavailability of three prototype fixed dose combination (FDC) tablet formulations of valsartan/hydrochlorothiazide/amlodipine (V/H/A) 160/12.5/5 mg relative to the free combination of 160 mg valsartan, 12.5 mg hydrochlorothiazide, and 5 mg amlodipine, and to assess safety and tolerability of the prototype formulations and the free combination.

4.1.1.2 Study design

This was a single center, open label, randomized, four period, four sequence, crossover study. The treatment periods were separated by a washout period of a minimum of 14 days. Each of the subjects was randomized to receive in one of the four sequences the following:

1. Single oral dose of 160/12.5/5 mg of V/H/A prototype I (treatment A).
2. Single oral dose of 160/12.5/5 mg of V/H/A prototype II (treatment B).
3. Single oral dose of 160/12.5/5 mg of V/H/A prototype III (treatment C).
4. Single oral dose of free combination of 160 mg valsartan, 12.5 mg of hydrochlorothiazide, and 5 mg of amlodipine (treatment D).

4.1.1.2.1 Study medication

1. Prototype I: 160/12.5/5 mg FDC valsartan/HCTZ/amlodipine tablet – Monolithic tablet – 1, Batch #AEUS/2005-0369
2. Prototype II: 160/12.5/5 mg FDC valsartan/HCTZ/amlodipine tablet – Monolithic tablet – 2, Batch #AEUS/2005-0370
3. Prototype III: 160/12.5/5 mg FDC valsartan/HCTZ/amlodipine tablet –Bilayer tablet - Batch #AEUS/2006-0115
4. Valsartan 160 mg (Diovan®) [commercial tablet formulation] Lot #F0299
Expiration : Jan 2008
5. Hydrochlorthiazide 12.5 mg (CSF) [hard gelatin capsule] Lot #H212JB
6. Amlodipine 5 mg (CSF) [over-encapsulated tablet] Lot #15172.2

4.1.1.2.2 Sample size estimation

A minimum of 6 subjects per treatment group are required to estimate a 90% CI with a width of approximately 41% of the estimated mean ratio.

4.1.1.2.3 Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, and 168h post dose.

4.1.1.2.4 Pharmacokinetic data analysis

Using noncompartmental methods, the following pharmacokinetic measures were determined for all three treatments.

C_{max} , AUC_{last} , AUC_{inf} , T_{max} , λ_z and $t_{1/2}$

4.1.1.2.5 Statistical data analysis

Log transformed pharmacokinetic measures of systemic exposure (C_{max} , AUC) were analyzed using ANOVA linear mixed effects model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect. Point estimates and associated 90 % confidence intervals (CI) were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means.

4.1.1.3 Safety assessments

Physical examination, vital signs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events reported were collected and evaluated.

4.1.1.4 Bioanalytical method

Plasma concentrations of V/H/A were measured simultaneously using a validated HPLC/MS/MS method. The performance measures of the assay are presented in **Table1**.

Table 1: Performance measures of V/H/A assay in study VEA489A2305 (Ref: Appendix 16.2.5, DMPK RCVEA489A2305)

	Valsartan	Hydrochlorothiazide	Amlodipine
Linearity	5 to 5000 ng/mL (weighted $1/x^2$, $r > 0.999$)	1 to 200 ng/mL (weighted $1/x^2$, $r > 0.999$)	0.025 to 10 ng/mL (weighted $1/x^2$, $r > 0.999$)
Precision (% CV)	2.5 to 4.4	2.4 to 4.4	4.1 to 6.8
Accuracy (% Bias)	-2.0 to 1.3	-0.3 to -1.0	0.9 to 3.2

Reviewer's comment:

The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

4.1.1.5 Study Results

4.1.1.5.1 Subject demographics

Thirty two subjects (eight per sequence) were enrolled in the study, and 26 subjects completed all four periods of the study. Of the six subjects who discontinued treatment, only one (subject # 5111) was withdrawn from the study due to adverse events (vehicular accident not related to the study). The subject demographics were uniform across treatment groups. The mean age and weight among the four groups ranged from 24.9 to 30.9 years (range of individual values: 20 to 43 years) and 73.9 to 77.3 Kg (range of individual values: 56.0 to 96.2 Kg), respectively.

4.1.1.5.2 Pharmacokinetic results

Pharmacokinetic data for analysis were available from 30, 27, 29, and 28 subjects for prototypes I, II, III and the free combination, respectively.

Tables 3(a) to 3(c) present the pharmacokinetic measures for the individual components in the three prototype formulations and the free combination. As seen in Table 3(a), systemic exposure to valsartan following administration of a single oral dose of prototype I (treatment A) appears to be comparable to that following administration of the free combination (treatment D). Peak plasma concentrations also appear to be similar between prototype I and the free combination.

Table 3(a): Summary of pharmacokinetic measures for valsartan (Ref: Tables 14.2-1.1 to 14.2-1.6)

Parameter	Treatment			
	Prototype I (n = 29)	Prototype II (n = 26)	Prototype III (n = 28)	Free Combination (n = 27)
AUC _{0-∞} (ng.h/mL)	26327 ± 10952 ^a (42%)	28163 ± 9541 (34%)	29146 ± 10134 ^b (35%)	26610 ± 13192 (50%)
AUC _{0-t} (ng.h/mL)	26019 ± 10822 (42%)	27781 ± 9581 (35%)	27465 ± 9772 (36%)	26355 ± 13180 (50%)
C _{max} (ng/mL)	3525 ± 1529 (43%)	3911 ± 1174 (30%)	3366 ± 1259 (37%)	3569 ± 1729 (49%)
t _{max} (hr) Median (min, max) (CV%)	3.0 — (39%)	3.0 — (40%)	3.0 — (48%)	3.0 — (34%)
t _{1/2} (hr)	18.3 ± 12.4 ^a (68%)	21.7 ± 20.8 (96%)	23.4 ± 27.2 ^b (116%)	15.4 ± 5.7 (37%)

b(4)

Note: Plasma concentrations in subject 5122 following administration of the free combination (treatment D) in period II of the study were 10-fold lower than that observed during other periods of the study. This was judged to be atypical and all PK data from subject 5122 were excluded from analysis. Results of statistical analysis with and without subject 5122 were presented. The 90% CI for AUC and C_{max} for all prototype formulations tested exceeded 80 to 125%. The 90% CIs for AUC and C_{max} for prototype I were 95 to 129% and 90 to 132%, respectively.

Reviewer's comment:

As seen in the plot below, plasma valsartan concentration versus time profile for subject 5122 following administration of the free combination (treatment D)

is atypical of the group (mean free comb, (■)). The justification for excluding all PK data from subject 5122 is acceptable. A comparison to the three prototype formulations is also provided in the plot.

Plasma valsartan concentration-time profile for subject 5122



b(4)

As seen in Table 3(b), systemic exposure to hydrochlorothiazide following administration of a single oral dose of prototypes I and III appear to be comparable to that following administration of the free combination.

Table 3(b): Summary of pharmacokinetic measures for hydrochlorothiazide (Ref: Tables 14.2-1.1 to 14.2-1.6)

Parameter	Treatment			
	Prototype I (n=30)	Prototype II (n=27)	Prototype III (n=29)	Free Combination (n=28)
AUC _{0-∞} (ng.h/mL)	517.6 ± 125.5 (24%)	542.1 ± 123.0 (23%)	522.8 ± 156.6 (30%)	516.4 ± 143.1 ^a (28%)
AUC ₀₋₁ (ng.h/mL)	496.0 ± 125.3 (25%)	519.9 ± 123.3 (24%)	500.3 ± 154.2 (31%)	476.8 ± 169.5 (36%)
C _{max} (ng/mL)	76.3 ± 21.7 (28%)	82.9 ± 23.8 (29%)	75.8 ± 24.0 (32%)	73.1 ± 25.5 (35%)
t _{max} (hr)				
Median (min, max) (CV%)	2.0 — (52%)	1.0 — (45%)	2.0 — (74%)	2.0 — (40%)
t _{1/2} (hr)	9.5 ± 1.8 (19%)	9.9 ± 1.7 (17%)	9.6 ± 1.4 (14%)	10.0 ± 1.2 ^a (12%)

b(4)

The exposure to amlodipine following administration of a single oral dose of prototypes I, II and III appear to be comparable to that following administration of the free combination (Table 3(c)).

Table 3(c): Summary of pharmacokinetic measures for amlodipine (Ref: Tables 14.2-1.1 to 14.2-1.6)

Parameter	Treatment			
	Prototype I (n=29)	Prototype II (n=27)	Prototype III (n=28)	Free Combination (n=27)
AUC _{0-∞} (ng.h/mL)	143.4 ± 45.5 (32%)	139.5 ± 45.1 (32%)	148.5 ± 46.3 (31%)	142.2 ± 50.6 (36%)
AUC ₀₋₄ (ng.h/mL)	130.6 ± 38.8 (30%)	127.5 ± 39.2 (31%)	137.0 ± 39.7 (29%)	130.9 ± 43.3 (33%)
C _{max} (ng/mL)	2.7 ± 0.6 (21%)	2.6 ± 0.7 (26%)	2.8 ± 0.6 (23%)	2.7 ± 0.7 (26%)
t _{max} (hr)				
Median	6.0 / _____	6.0 _____ ,	6.0 _____	6.0 _____
(min, max)	(25%)	(22%)	(30%)	(29%)
(CV%)				
t _{1/2} (hr)	45.1 ± 9.0 (20%)	46.8 ± 13.3 (28%)	43.2 ± 9.0 (20%)	43.4 ± 8.0 (18%)

b(4)

Note:

1. Pre-dose plasma amlodipine concentrations were observed in nine subjects (5 in sequence II, 2 in sequence I, and 2 in sequence IV) in the study. The observed values were < 5% of C_{max} and were retained as such in the analysis.
2. Plasma concentrations in subject 5112 following administration of treatment D in period III of the study were 10-fold lower than that observed during other periods of the study. This was judged to be atypical and all PK data from subject 5112 were excluded from analysis. Results of statistical analysis with and without subject 5112 were presented. The 90% CIs for AUC and C_{max} all prototype formulations tested lie within 80 to 125%.

Reviewer's comment:

Handling of pre-dose concentrations follows the recommendations in 'Guidance for Industry: Bioavailability and Bioequivalence Studies for orally Administered Drug Products – General Considerations' and is acceptable.

4.1.1.5.3 Statistical analysis results

Table 4 presents a summary of the results of the statistical analysis of pharmacokinetic exposure measures for the prototype formulations. As seen in Table 4, for prototype I, the 90% CI of the ratio (AUC_{test}/AUC_{ref}) lies within 80 to 125%, and therefore do not significantly differ in the extent of exposure.

Table 4: Summary of results of the statistical analysis of PK measures (Ref: Tables 14.2-1.1 to 14.2-1.6).

Analyte	PK parameter	Ratio of geometric means (90% CI)		
		VEA489A Prototype I	VEA489A Prototype II	VEA489A Prototype III
Valsartan	AUC ₍₀₋₄₎	1.02 (0.88-1.19)	1.13 (0.97-1.32)	1.10 (0.95-1.28)
	AUC _(0-inf)	1.04 (0.90-1.20)	1.15 (0.99-1.33)	1.19 (1.03-1.39)
	C _{max}	1.00 (0.84-1.20)	1.17 (0.97-1.40)	0.99 (0.83-1.18)
HCTZ	AUC ₍₀₋₄₎	0.99 (0.94-1.04)	1.06 (1.00-1.11)	1.00 (0.95-1.05)
	AUC _(0-inf)	0.99 (0.95-1.04)	1.05 (1.00-1.10)	1.00 (0.95-1.05)
	C _{max}	1.00 (0.91-1.10)	1.08 (0.99-1.19)	0.99 (0.90-1.09)
Amlodipine	AUC ₍₀₋₄₎	1.00 (0.94-1.07)	0.97 (0.90-1.04)	1.05 (0.98-1.13)
	AUC _(0-inf)	1.01 (0.94-1.08)	0.97 (0.91-1.04)	1.05 (0.98-1.13)
	C _{max}	1.03 (0.96-1.11)	0.99 (0.92-1.07)	1.06 (0.98-1.14)

4.1.1.5.4 Safety results

The incidence of adverse events (AEs) appeared to be uniform between treatment groups. Fourteen of the 32 subjects enrolled in the study experienced adverse events. A total of 34 AEs were reported, of which the investigators consider approximately half to be related to the study drug. Headache was the most commonly reported side effects.

4.1.1.6 Conclusions

- The rate (C_{max}) and extent (AUC) of absorption of V/H/A following administration of a single dose of prototype I are not significantly different from that following administration of a single dose of the free combination.
- Exforge HCT prototype I is bioequivalent to the free combination of V/H/A.

4.1.2 Study VEA489A2306 (Bioequivalence – 160/25/10)

An open-label, randomized, single dose, three period, crossover design study to determine the relative bioavailability of two prototype 160/25/10 mg fixed combination valsartan/HCTZ/amlodipine tablets to a free combination of phase III-clinical service forms (CSFs) of 160 mg valsartan, 25 mg HCTZ, and 10 mg amlodipine.

Protocol number: CVEA489A2306

Investigator: _____

Study site: _____, _____, _____

b(4)

Study dates: 04/22/2006 to 05/31/2006

4.1.2.1 Objectives

The objectives of the study were to determine the bioavailability of two prototype fixed dose combination (FDC) tablet formulations of valsartan/hydrochlorothiazide/amlodipine (V/H/A) 160/25/10 mg relative to the free combination of 160 mg valsartan, 25 mg hydrochlorothiazide, and 10 mg amlodipine, and to assess safety and tolerability of the prototype formulations and the free combination.

4.1.2.2 Study design

This was a single center, open label, randomized, three period, three sequence, crossover design study. The treatment periods were separated by a washout period of a minimum of 14 days. Each of the subjects was randomized to one of the three sequences to receive the following:

1. Single oral dose of 160/25/10 mg of V/H/A prototype I (treatment A).
2. Single oral dose of 160/25/10 mg of V/H/A prototype II (treatment B).
3. Single oral dose of free combination of 160 mg valsartan, 25 mg of hydrochlorothiazide, and 10 mg of amlodipine (treatment C).

4.1.2.2.1 Study medication

1. Prototype I: 160/25/10 mg fixed combination valsartan/HCTZ/amlodipine tablet – Monolithic tablet – 1, Batch #AEUS/2006-0002
2. Prototype II: 160/25/10 mg fixed combination valsartan/HCTZ/amlodipine tablet – Monolithic tablet – 2, Batch #AEUS/2006-0003
3. Valsartan 160 mg (Diovan®) [commercial tablet formulation] Lot #F0295
Expiration date:
4. Hydrochlorothiazide 25 mg (CSF) [hard gelatin capsule] Lot #H211.JB
5. Amlodipine 10 mg (CSF) [over-encapsulated tablet] Lot #15172.3

4.1.2.2.2 Sample size estimation

A minimum of eight subjects per sequence are required to estimate a 90% CI with a width of approximately 41% of the estimated mean ratio.

4.1.2.2.3 Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, and 168h post dose.

4.1.2.2.4 Pharmacokinetic data analysis

Using noncompartmental methods, the following pharmacokinetic measures were determined for all three treatments.

C_{max} , AUC_{last} , AUC_{inf} , T_{max} , λ_z and $t_{1/2}$

4.1.2.2.5 Statistical data analysis

Log transformed pharmacokinetic measures of systemic exposure (C_{max} , AUC) were analyzed using ANOVA linear mixed effects model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect. Point estimates and associated 90 % confidence intervals (CI) were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means.

4.1.2.3 Safety assessments

Physical examination, vital signs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events reported were collected and evaluated.

4.1.2.4 Bioanalytical method

Plasma concentrations of V/H/A were measured simultaneously using a validated HPLC/MS/MS method. The performance measures of the assay are presented in **Table 1**.

Table 1: Performance measures of V/H/A assay in study VEA489A2306 (Ref: Appendix 16.2.5, DMPK RCVEA489A2306)

	Valsartan	Hydrochlorothiazide	Amlodipine
Linearity	5 to 5000 ng/mL (weighted $1/x^2$, $r > 0.999$)	1 to 200 ng/mL (weighted $1/x^2$, $r > 0.999$)	0.025 to 10 ng/mL (weighted $1/x^2$, $r > 0.999$)
Precision (% CV)	2.4 to 5.9	2.6 to 5.2	7.2 to 12.4
Accuracy (% Bias)	-0.8 to 0.7	-1.9 to 1.7	1.7 to 4.7

Reviewer's comment:

The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

4.1.2.5 Study Results

4.1.2.5.1 Subject demographics

Thirty subjects (10 per sequence) were enrolled in the study, and 28 subjects completed all three periods of the study. Of the two subjects who discontinued treatment, one (subject # 5123) withdrew consent and the other (subject # 5125) was lost to follow up on

day 16 of the study. The subject demographics were uniform across treatment groups/cohorts. The mean age and weight among the three groups ranged from 25.8 to 32.7 years (range of individual values: 19 to 44 years) and 73.7 to 79.5 Kg (range of individual values: 54.3 to 94.2 Kg), respectively.

4.1.2.5.2 Pharmacokinetic results

Tables 2(a) to (c) present the pharmacokinetic measures for each of the components in the three prototype formulations and the free combination.

Table 2(a): Summary of pharmacokinetic measures for valsartan (Ref: Tables 14.2-1.1 to 14.2-1.6)

Treatment	AUC _{0-t} (µg-h/mL)	AUC _{0-∞} (µg-h/mL)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr)
	Mean ± SD (CV%)	Mean ± SD (CV%)	Mean ± SD (CV%)	Median (min, max)	Mean ± SD (CV%)
Prototype I	32.62 ± 12.94 (39.7%)	33.94 ± 12.84 (37.8%)	5.01 ± 2.09 (41.7%)	2.9 ————	14.4 ± 7.2 (50.1%)
Prototype II	35.78 ± 13.85 (38.7%)	36.36 ± 13.95 (38.4%)	5.45 ± 2.30 (42.2%)	3.2 ————	14.2 ± 6.5 (45.8%)
Free combination	34.68 ± 13.08 (37.7%)	35.28 ± 13.26 (37.6%)	5.26 ± 2.09 (39.6%)	2.8 ————	15.0 ± 7.7 (51.0%)

b(4)

Table 2(b): Summary of pharmacokinetic measures for hydrochlorothiazide (Ref: Tables 14.2-1.1 to 14.2-1.6)

Treatment	AUC _{0-t} (µg-h/mL)	AUC _{0-∞} (µg-h/mL)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr)
	Mean ± SD (CV%)	Mean ± SD (CV%)	Mean ± SD (CV%)	Median (min, max)	Mean ± SD (CV%)
Prototype I	1015.7 ± 223.4 (22.0%)	1049.5 ± 225.4 (21.5%)	153.5 ± 64.1 (41.8%)	1.8 ————	11.3 ± 1.6 (14.1%)
Prototype II	1025.8 ± 176.3 (17.2%)	1064.7 ± 180.5 (16.9%)	156.0 ± 50.6 (32.4%)	1.8 ————	11.1 ± 1.2 (10.6%)
Free combination	1004.5 ± 242.4 (24.1%)	1037.8 ± 245.8 (23.7%)	154.3 ± 50.5 (32.7%)	2.1 ————	10.9 ± 1.7 (15.5%)

b(4)

Table 2(c): Summary of pharmacokinetic measures for amlodipine (Ref: Tables 14.2-1.1 to 14.2-1.6)

Treatment	AUC _{0-t} (µg·h/mL)	AUC _{0-∞} (µg·h/mL)	C _{max} (µg/mL)	t _{max} (hr)	t _{1/2} (hr)
	Mean ± SD (CV%)	Mean ± SD (CV%)	Mean ± SD (CV%)	Median (min, max)	Mean ± SD (CV%)
Prototype I	303.2 ± 116.7 (38.5%)	326.0 ± 130.4 (40.0%)	5.6 ± 1.7 (31.3%)	8.9 —	40.5 ± 7.1 (17.7%)
Prototype II	309.5 ± 100.7 (32.5%)	332.2 ± 111.6 (33.6%)	5.7 ± 1.7 (29.5%)	9.1 —	40.5 ± 6.3 (15.5%)
Free combination	293.3 ± 98.1 (33.5%)	316.3 ± 108.8 (34.4%)	5.5 ± 1.6 (29.2%)	8.7 —	42.0 ± 9.5 (22.5%)

b(4)

As seen in **Tables 2(a)-(c)**, both systemic exposure and peak plasma levels for the individual components following administration of a single dose of prototypes I and II are comparable to that observed following administration of a single dose of the free combination.

4.1.2.5.3 Statistical analysis results

Table 3 presents a summary of the results of the statistical analysis of pharmacokinetic exposure measures for the prototype formulations. As seen in **Table 3**, for prototypes I and II, the 90% CI of the ratios for AUC and C_{max} (test/reference) lies within 80 to 125%, and therefore do not significantly differ in the extent of exposure.

Table 3: Summary of results of the statistical analysis of PK measures (Ref: Tables 14.2-1.1 to 14.2-1.6).

Analyte	PK parameter	Ratio of geometric means (90% CI)	
		Prototype I	Prototype II
Valsartan	AUC _(0-t) (µg·h/mL)	0.96 (0.86, 1.06)	1.05 (0.94, 1.16)
	AUC _(0-∞) (µg·h/mL)	0.99 (0.89, 1.10)	1.07 (0.96, 1.19)
	C _{max} (µg/mL)	0.97 (0.85, 1.11)	1.03 (0.91, 1.17)
HCTZ	AUC _(0-t) (ng·h/mL)	1.01 (0.96, 1.06)	1.04 (0.99, 1.09)
	AUC _(0-∞) (ng·h/mL)	1.00 (0.96, 1.05)	1.03 (0.98, 1.08)
	C _{max} (ng/mL)	0.97 (0.89, 1.06)	1.01 (0.93, 1.10)
Amlodipine	AUC _(0-t) (ng·h/mL)	1.02 (0.94, 1.11)	1.06 (0.97, 1.15)
	AUC _(0-∞) (ng·h/mL)	1.02 (0.93, 1.11)	1.05 (0.97, 1.14)
	C _{max} (ng/mL)	1.02 (0.94, 1.11)	1.04 (0.96, 1.13)

4.1.2.5.4 Safety results

The incidence of AEs appeared to be uniform between treatment groups. Ten of the 30 subjects enrolled in the study experienced adverse events. Headache was the most commonly reported side effects.

4.1.2.6 Conclusions

- The rate (C_{max}) and extent (AUC) of absorption of V/H/A following administration of a single dose of prototypes I and II are not significantly different from that following administration of a single dose of the free combination.
- Exforge HCT prototypes I and II are bioequivalent to the free combination of V/H/A.

4.1.3 Study VEA489A2310 (Food Effect – 320/25/10)

An randomized, open-label, single-dose, two-period crossover design study in healthy subjects to evaluate the effect of food on the bioavailability of valsartan /hydrochlorothiazide /amlodipine 320/25/10 mg fixed combination Final Market Image (FMI) tablet.

Protocol number: CVEA489A2310

Investigator: _____

Study site: _____

b(4)

Study dates: 06/25/2007 to 08/01/2007

4.1.3.1 Objectives

The objective of this study was to evaluate the effect of food on the bioavailability of valsartan/hydrochlorothiazide/amlodipine 320/25/10 mg FMI tablet.

4.1.3.2 Study design

This was a single center, open label, randomized, two period, crossover design study. The treatment periods were separated by a washout period of a minimum of 14 days. Each of the subjects was randomized to receive the following:

1. Fixed combination valsartan/HCTZ/amlodipine FMI tablet (320/25/10 mg) under fasted conditions
2. Fixed combination valsartan/HCTZ/amlodipine FMI tablet (320/25/10 mg) within 30 minutes of a standard FDA high-fat breakfast. The high-fat breakfast consisted of the following: 2 eggs cooked in butter, 2 strips of bacon, 2 slices of toast with 2 pats of butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk (meal was approximately equivalent to 150, 250 and 500 calories from protein, carbohydrate and fat, respectively).

Reviewer's comment:

The composition and calorie content of the high fat meal follows the 'Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug products – General Considerations' and is acceptable.

4.1.3.2.1 Study medication

FMI 320/25/10 mg fixed combination valsartan/HCTZ/amlodipine tablet, Batch #AEUS/2006-0366

4.1.3.2.2 Sample size estimation

A minimum of 16 subjects per sequence are required to estimate a 90% CI with a width of approximately 41% of the estimated mean ratio.

4.1.3.2.3 Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, and 168h post dose.

4.1.3.2.4 Pharmacokinetic data analysis

Using noncompartmental methods, the following pharmacokinetic measures were determined for all three treatments.

C_{max} , AUC_{last} , AUC_{inf} , T_{max} , λ_z and $t_{1/2}$

4.1.3.2.5 Statistical data analysis

Log transformed pharmacokinetic measures of systemic exposure (C_{max} , AUC) were analyzed using ANOVA linear mixed effects model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect. Point estimates and associated 90 % confidence intervals (CI) were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means.

4.1.3.3 Safety assessments

Physical examination, vital signs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events reported were collected and evaluated.

4.1.3.4 Bioanalytical method

Plasma concentrations of V/H/A were measured simultaneously using a validated HPLC/MS/MS method. The performance measures of the assay are presented in **Table 1**.

Table 1: Performance measures of V/H/A assay in study VEA489A2310 (Ref: Appendix 16.2.5, DMPK RCVEA489A2310)

	Valsartan	Hydrochlorothiazide	Amlodipine
Linearity	5 to 5000 ng/mL (weighted $1/x^2$, $r > 0.999$)	1 to 200 ng/mL (weighted $1/x^2$, $r > 0.999$)	0.025 to 10 ng/mL (weighted $1/x^2$, $r > 0.999$)
QCs:			
Precision (% CV)	2.3 to 4.0	2.8 to 6.4	4.5 to 7.5
Accuracy (% Bias)	-2.9 to 1.8	-1.3 to 0.8	0.3 to 2.4
Dilution QC:			
Concentration	24000 ng/mL	480 ng/mL	24 ng/mL
Precision (% CV)	2.5	1.2	4.9
Accuracy (% Bias)	3.8	-2.9	-1.3

Reviewer's comment:

The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

4.1.3.5 Study Results

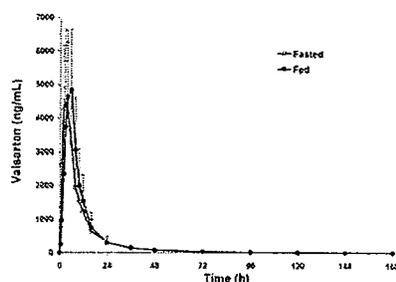
4.1.3.5.1 Subject demographics

Thirty six subjects (18 per sequence) were enrolled in the study, and 33 subjects completed both periods of the study. Of the three subjects who discontinued treatment, one (subject # 5104) withdrew consent after period 2 and the others (subject # 5109 and 5115) were discontinued from the study due to abnormal lab values after period 1. The subject demographics were uniform across treatment groups/cohorts. The mean age and weight were 30.9 years (range: 18 to 45 years) and 79.38 Kg (56.2 to 102 Kg), respectively.

4.1.3.5.2 Pharmacokinetic results

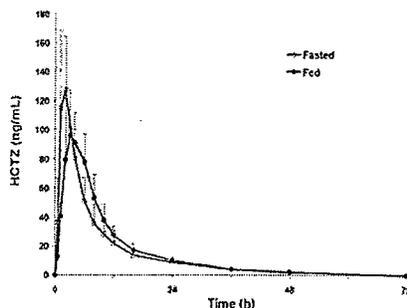
Figures 1(a)-(c) present a graphical comparison of plasma concentration versus time profiles for each of the components in the fed and fasted condition, along with the relevant pharmacokinetic measures.

(a) Valsartan



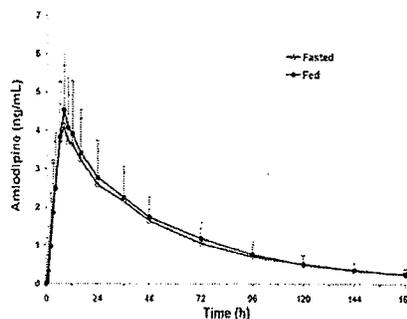
PK Parameter	Arithmetic mean plus minus SD* (CV%) for N=35	
	Fed (test)	Fasting (reference)
t_{max} (h)*	4.0 (1.0 – 8.0)	3.0 (1.0 – 6.0)
C_{max} (ng/mL)	5579 ± 1724 (30.9)	5176 ± 2058 (39.8)
AUC_{0-t} (h*ng/mL)	49432 ± 16705 (33.8)	45233 ± 19981 (44.2)
$t_{1/2}$ (h)	14.5 ± 6.3 (43.0)	13.2 ± 6.2 (47.1)
$AUC_{0-\infty}$ (h*ng/mL)	49919 ± 16586 (33.2)	45610 ± 19961 (43.8)

(b) Hydrochlorothiazide



PK Parameter	Arithmetic mean ± SD* (CV%) for N=35	
	Fed (test)	Fasting (reference)
t_{max} (h)*	3.0 (1.0 – 8.0)	2.0 (1.0 – 4.0)
C_{max} (ng/mL)	113.2 ± 23.5 (20.8)	136.7 ± 43.1 (31.6)
AUC_{0-t} (h*ng/mL)	1042.4 ± 135 (12.9)	980.3 ± 272.1 (27.8)
$t_{1/2}$ (h)	10.7 ± 1.5 (13.7)	12.0 ± 3.0 (24.9)
$AUC_{0-\infty}$ (h*ng/mL)	1076.4 ± 140.9 (13.1)	1019 ± 273.7 (26.9)

(c) Amlodipine



PK Parameter	Arithmetic mean ± SD* (CV%) for N=35	
	Fed (test)	Fasting (reference)
t_{max} (h)*	8.0 (4.0 – 13.0)	8.0 (6.0 – 16.0)
C_{max} (ng/mL)	4.8 ± 1.6 (33)	4.4 ± 1.6 (36.4)
AUC_{0-t} (h*ng/mL)	217.8 ± 72.7 (33.4)	207.2 ± 72.8 (35.1)
$t_{1/2}$ (h)	43.3 ± 9.0 (20.5)	41.8 ± 9.4 (22.4)
$AUC_{0-\infty}$ (h*ng/mL)	237.1 ± 78.7 (33.2)	223.0 ± 80.7 (36.2)

Figure 1: Plots of the mean (\pm SD) plasma concentration versus time for (a) valsartan (b) hydrochlorothiazide and (c) amlodipine. Open circles represent the fasted state and the closed circles represent the fed state. The relevant pharmacokinetic measures for the individual components are presented in the panel to the right.

4.1.3.5.3 Statistical analysis results

Table 2 presents a summary of the results of the statistical analysis of pharmacokinetic exposure measures. As seen in **Table 2**, both AUC and C_{max} for valsartan exceed the default bioequivalence limits of 80 to 125%. Peak plasma concentrations of HCT following administration of a single dose under fed conditions are significantly lower than that in the fasted state.

Table 4: Summary of results of the statistical analysis of PK measures (Ref: Tables 14.2-2.1 to 14.2-2.3).

	Geometric mean		Geometric mean ratio	
	Fed (n=35)	Fasting (n=35)	Estimate	90% CI
Valsartan				
C_{max} (ng/mL)	5327.61	4739.52	1.12	0.98 - 1.29
AUC _{0-t} (hr*ng/mL)	46645.61	40982.76	1.14	0.99 - 1.31
AUC _{0-∞} (hr*ng/mL)	47199.80	41429.90	1.14	0.99 - 1.31
Hydrochlorothiazide				
C_{max} (ng/mL)	110.72	128.60	0.86	0.79 - 0.93
AUC _{0-t} (hr*ng/mL)	1031.83	940.63	1.10	1.02 - 1.18
AUC _{0-∞} (hr*ng/mL)	1064.98	980.53	1.09	1.02 - 1.16
Amlodipine				
C_{max} (ng/mL)	4.64	4.18	1.11	1.05 - 1.18
AUC _{0-t} (hr*ng/mL)	208.65	191.96	1.09	1.03 - 1.15
AUC _{0-∞} (hr*ng/mL)	228.31	208.89	1.09	1.04 - 1.15

Reviewer's comment:

Given the intersubject variability in the PK of valsartan and hydrochlorothiazide, the observed statistically significant effect of food on PK is likely to not affect efficacy or safety, and are therefore judged not to be of any clinical significance.

4.1.3.5.4 Safety results

Twelve of the 36 subjects enrolled in the study experienced adverse events. Headache was the most commonly reported side effects.

4.1.3.6 Conclusions

Food dose not significantly affect the pharmacokinetics of V, H, and A following administration of a singled dose of Exforge HCT.

4.1.4 Study VEA489A 2104 (Pharmacokinetic drug interaction)

A multi-center, multiple dose, open-label, four-cohort, parallel design study to assess the pharmacokinetic drug interaction following co-administration of valsartan, hydrochlorothiazide and amlodipine in patients with hypertension.

Protocol number: CVEA489A2104

Investigators and sites: This study was conducted at five centers in India. The investigator names and the corresponding sites are listed below.

1.

2.

3.

4.

5.

b(4)

Study dates: 09/26/2007 to 03/18/2008

4.1.4.1 Objectives

The objectives of the study were to assess the potential for pharmacokinetic drug interaction between valsartan, hydrochlorothiazide and amlodipine at steady state when administered together as a triple combination, and to evaluate safety and tolerability of the triple combination in patients with hypertension.

4.1.4.2 Study Design

This was a multi-center, open label, four cohort, parallel design study conducted in patients with hypertension. Following a screening period (day -21 to -2) and baseline observations (day -1), patients meeting the inclusion / exclusion criteria were allocated to one of the four treatment cohorts shown in **Table 1**.

Table 1: Summary of the study design and dosing schedule for VEA489A2104.

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Treatment	V/H	V/A	H/A	V/H/A
Days 1 - 6	V: 1 x 160 mg H: 1 x 12.5 mg	V: 1 x 160 mg A: 1 x 5 mg	H: 1 x 12.5 mg A: 1 x 5 mg	V: 1 x 160 mg H: 1 x 12.5 mg A: 1 x 5 mg
	On day 6 all patients were admitted to the clinic at least 16 h prior to dosing on day 7, and discharged 48 h post dosing.			
Days 7 to 17	V: 2 x 160 mg H: 2 x 12.5 mg	V: 2 x 160 mg A: 2 x 5 mg	H: 2 x 12.5 mg A: 2 x 5 mg	V: 2 x 160 mg H: 2 x 12.5 mg A: 2 x 5 mg
	On day 16 all patients were admitted to the clinic at least 16 h prior to dosing on day 17. Safety evaluations were performed.			
Day 17	PK sampling for measuring V, A, and H in all groups.			
	Study completion evaluation.			

Patients who were previously receiving a two drug therapy for the management of hypertension and who were to be enrolled in any of the dual combination cohorts, were directly switched to the dual combination. Similarly, patients on triple combination therapy, who were enrolled in cohort 4 were directly switched to V/H/A. The study design was similar to that of the pivotal efficacy study.

4.1.4.2.1 Study medication

Valsartan (Diovan ®): Novartis Pharma, Batch no. S0216

Hydrochlorothiazide (Aquazide ®): Sun Pharmaceutical Industries, Batch no. AD70233

Amlodipine (Amlogard ®): Pfizer Ltd., Batch no. 620-05034

4.1.4.2.2 Pharmacokinetic sampling

Pre-dose blood samples were collected on days 6, 10, 15 and 16 of the study. On day 17, blood samples were collected at pre-dose and 0.25h, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h, and 24h post dosing.

Reviewer's comment:

The sampling duration on day 17 spans less than one half-life for amlodipine. An accurate characterization of systemic exposure (AUC) to amlodipine will therefore not be possible. However, given that the patients are at steady state with respect to amlodipine by day 17 of the study, accumulation of amlodipine can be detected in this initial phase. The sampling times are therefore acceptable.

4.1.4.2.3 Sample size estimation

A minimum of 25 subjects per treatment group are required to estimate a 90% confidence interval of 0.77 to 1.3.

4.1.4.3 Data Analysis

4.1.4.3.1 Pharmacokinetic data analysis

Using non-compartmental methods, the following pharmacokinetic measures were determined for valsartan, hydrochlorothiazide and amlodipine in all treatment cohorts.

AUC_{0-τ}, C_{ss max}, C_{ss min}, C_{ss average}, and t_{ss max}.

4.1.4.3.2 Statistical data analysis

Log transformed PK measures (geometric means) of systemic exposure, AUC and C_{max} were analyzed using an AVOVA linear mixed effects model in SAS. Concomitant hypertensive pre-treatments, nested within treatment, and hypertension status were included in the model. Posthoc treatment contrasts, with the triple combination as the reference, were also performed.

4.1.4.4 Safety assessments

Physical examination, vital signs, clinical laboratory tests, ECG assessments, and reports of adverse events and serious adverse events were performed and evaluated to assess subject safety.

4.1.4.5 Bioanalytical method

Performance measures for the assay specific to study VEA489A2401 were not provided.

Reviewer's comment:

Validation results for the assay are presented in section 2.6 of the QBR. The assay met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

4.1.4.6 Study Results

4.1.4.6.1 Subject demographics

One hundred and eleven patients were enrolled in the study and 101 completed the study. Four of the 10 patients who did not complete the study were withdrawn due to adverse events. Three patients had blood pressure < 110/70, and were withdrawn from the study as the dose could not be increased as per protocol. One patient withdrew consent and two were lost to follow up. Tables 2(a) and 2(b) presents a summary of subject demographics, and a summary of hypertensive medication received prior to enrollment in study VEA489A2104, respectively.

Table 2(a): Summary of subject demographics for study VEA489A2401.

		Cohort 1 (V/H) N = 30	Cohort 2 (V/A) N = 28	Cohort 3 (H/A) N = 26	Cohort 4 (V/H/A) N = 27	Total N = 111
Age (years)	Mean	44.5	42.8	44.2	45.7	44.3
	SD	10.00	10.71	9.67	7.15	9.43
	Median	45.0	45.0	45.5	45.0	45.0
	Range	21-59	22-59	26-59	35-59	21-59
Gender – n (%)	Male	23(76.7 %)	22(78.6 %)	21(80.8 %)	13(48.1 %)	79(71.2 %)
	Female	7(23.3 %)	6(21.4 %)	5(19.2 %)	14(51.9 %)	32(28.8 %)
Race – n (%)	Asian	30(100 %)	28(100 %)	26(100 %)	27(100 %)	111(100 %)
Weight (kg)	Mean	64.62	63.41	67.27	64.37	64.88
	SD	7.308	9.309	6.892	8.659	8.115
	Median	62.00	61.50	67.90	65.00	64.90
	Range	53.8-80	50-87	56.8-87	50.7-82.3	50-87
Height (cm)	Mean	164.5	163.8	165.0	160.1	163.4
	SD	8.70	7.02	7.75	8.00	8.02
	Median	164.0	163.0	167.0	160.0	164.0
	Range	148-183	150-186	147-176	145-177	145-186
BMI (kg/m ²)	Mean	23.961	23.621	24.800	25.131	24.356
	SD	2.7756	2.8852	2.8487	3.1715	2.9445
	Median	23.151	23.564	24.378	24.974	24.160
	Range	19.94-29.21	18.93-29.30	20.52-29.82	19.32-32.89	18.93-32.89

Table 2(b): Summary of prior antihypertensive therapy for study VEA489A2401.

		Cohort 1 (V/H) N = 30	Cohort 2 (V/A) N = 28	Cohort 3 (H/A) N = 26	Cohort 4 (V/H/A) N = 27	Total N = 111
Antihypertensive medications – n (%)	0	10(33.3 %)	15(53.6 %)	11(42.3 %)		36(32.4 %)
	1	8(26.7 %)	3(10.7 %)	5(19.2 %)		16(14.4 %)
	2	12(40.0 %)	10(35.7 %)	10(38.5 %)	16(59.3 %)	48(43.2 %)
	3				11(40.7 %)	11(9.9 %)
BP Controlled? – n (%)	No	17(56.7 %)	17(60.7 %)	16(61.5 %)	16(59.3 %)	66(59.5 %)
	Yes	13(43.3 %)	11(39.3 %)	10(38.5 %)	11(40.7 %)	45(40.5 %)
Assigned Therapy – n (%)	2-drug therapy	30(100 %)	28(100 %)	26(100 %)		84(75.7 %)
	3-drug therapy				27(100 %)	27(24.3 %)

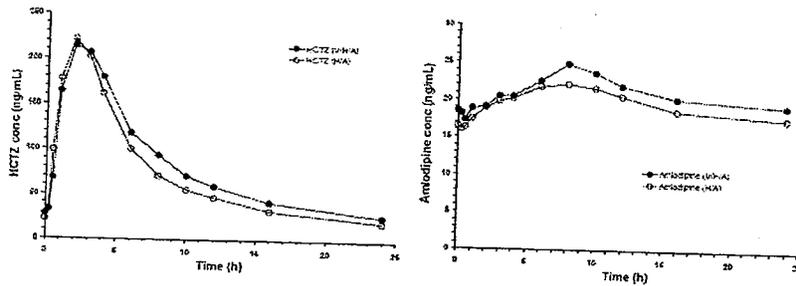
4.1.4.6.2 Pharmacokinetic results

Pharmacokinetic data for analysis were available from 25, 23, 23, and 23 subjects for cohorts I (V/H), II (V/A), III (H/A) and IV (V/H/A), respectively.

Figure 1 presents a graphical comparison of the average plasma concentration versus time profiles for the dual and the triple combinations, for each of the components in the FDC, along with the relevant pharmacokinetic measures.

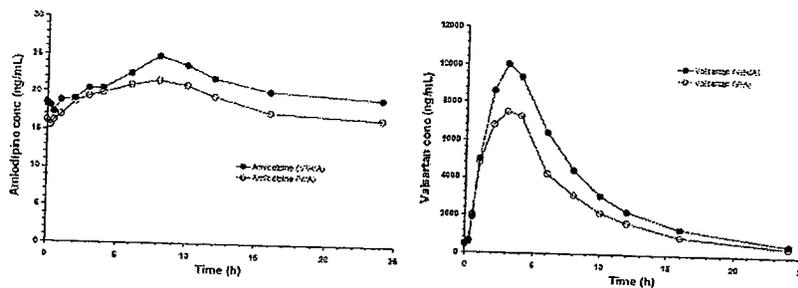
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(a) Effect of valsartan on the disposition of HCT and amlodipine



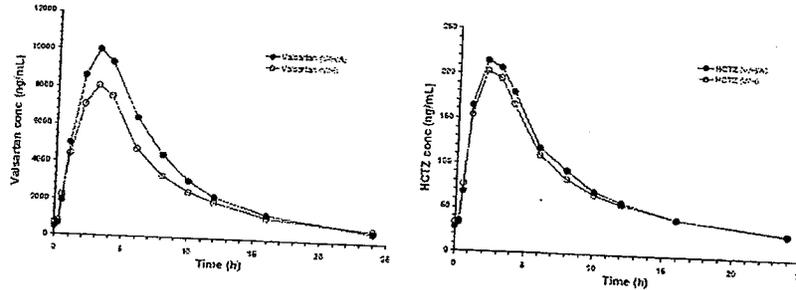
PK Parameter	HCTZ		Amlodipine	
	V/H/A	H/A	V/H/A	H/A
Subject (N)	23	23	23	23
AUC _{0-t} (ng*h/mL)	1969.2 ± 868.3 (44%)	1731.4 ± 720 (42%)	504.7 ± 119 (24%)	469.5 ± 172 (37%)
C _{ssmax} (ng/mL)	226.3 ± 65.6 (29%)	256.5 ± 92.3 (36%)	25.7 ± 5.5 (21%)	23 ± 7.9 (34%)
T _{ssmax} (h)*	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	8.0 (3.0, 16.1)	8.0 (3.0, 12.0)
C _{ssmin} (ng/mL)	26.1 ± 25.6 (98%)	20.4 ± 15 (73%)	16.2 ± 5.6 (35%)	15.5 ± 6.3 (40%)
C _{ssavg} (ng/mL)	82 ± 36.2 (44%)	72.1 ± 30 (42%)	21 ± 4.95 (24%)	19.6 ± 7.2 (37%)

(b) Effect of HCT on amlodipine and valsartan



PK Parameter	Valsartan		Amlodipine	
	V/H/A	V/A	V/H/A	V/A
Subject (N)	23	23	23	23
AUC _{0-t} (ng*h/mL)	82687 ± 43225 (52%)	61652 ± 28718 (47%)	504.7 ± 119 (24%)	450 ± 111.5 (25%)
C _{ssmax} (ng/mL)	10777 ± 4145 (38%)	8348 ± 3125 (37%)	25.7 ± 5.5 (21%)	22.4 ± 5.5 (24%)
T _{ssmax} (h)*	3 (2.0, 6.0)	3.0 (1.0, 4.5)	8.0 (3.0, 16.1)	8.0 (3.0, 12.75)
C _{ssmin} (ng/mL)	444 ± 356 (80%)	336 ± 188 (56%)	16.2 ± 5.6 (35%)	15 ± 3.81 (25%)
C _{ssavg} (ng/mL)	3445 ± 1801 (52%)	2569 ± 1197 (47%)	21 ± 4.95 (24%)	18.75 ± 4.7 (25%)

(c) Effect of amlodipine on valsartan and HCT



PK Parameter	Valsartan		HCTZ	
	V/H/A	V/H	V/H/A	V/H
Subject (N)	23	25	23	25
AUC _{0-τ} (ng*h/mL)	82687 ± 43225 (52%)	68188 ± 33241 (49%)	1969.2 ± 868.3 (44%)	1876.5 ± 838 (45%)
C _{ssmax} (ng/mL)	10777 ± 4145 (38%)	8677 ± 3255 (37%)	226.3 ± 65.6 (29%)	219 ± 76.7 (35%)
T _{ssmax} (h)*	3 (2.0, 6.0)	3.0 (1.75, 6.0)	2.0 (1.0, 3.0)	2.0 (0.25, 4.0)
C _{ssmin} (ng/mL)	444 ± 356 (80%)	573 ± 670 (117%)	26.1 ± 25.6 (98%)	27.4 ± 20.7 (75%)
C _{ssavg} (ng/mL)	3445 ± 1801 (52%)	2841 ± 1385 (49%)	82 ± 36.2 (44%)	78.2 ± 35 (45%)

Figure 1: Plots of the average plasma concentration versus time for (a) HCT and amlodipine (b) amlodipine and valsartan and (c) valsartan and HCT. Open circles represent the dual combination and the closed circles represent the triple combination. The relevant pharmacokinetic measures for the individual components are presented below the plot. (Ref:)

As seen in **Figure 1**, the systemic exposure to the individual components following administration of the triple combination exceeded that following administration of the dual combinations. With the exception of HCT in the presence of valsartan and amlodipine, peak plasma concentrations observed following administration of the triple combination exceeded that following administration of the dual combination.

4.1.4.6.3 Statistical analysis results

Tables 3(a)-(c) present the results of the statistical analysis of pharmacokinetic exposure measures for the individual components.

Table 3(a): Summary of the statistical analysis for HCT and amlodipine.

		Adjusted geometric mean		Geometric mean ratio ³	90% CI for ratio ³
		V / H / A ¹ N = 23	H / A ² N = 23		
HCTZ	AUC _{0-τ} (ng.h/mL)	1868.6	1726.1	1.08	0.89 - 1.32
	C _{ssmax} (ng/mL)	219.3	264.7	0.83	0.69 - 0.99
Amlodipine	AUC _{0-τ} (ng.h/mL)	494.8	453.6	1.09	0.90 - 1.32
	C _{ssmax} (ng/mL)	25.1	22.8	1.10	0.92 - 1.32

Table 3(b): Summary of the statistical analysis for amlodipine and valsartan.

		Adjusted geometric mean		Geometric mean ratio ³	90% CI for ratio ³
		V / H / A ¹ N = 23	V / A ² N = 23		
Valsartan	AUC _{0-τ} (ng.h/mL)	73385.6	58628	1.25	0.98 - 1.59
	C _{ssmax} (ng/mL)	9926.6	8136.3	1.22	0.98 - 1.52
Amlodipine	AUC _{0-τ} (ng.h/mL)	494.8	451	1.10	0.91 - 1.33
	C _{ssmax} (ng/mL)	25.1	22.8	1.10	0.92 - 1.32

Table 3(c): Summary of the statistical analysis for valsartan and HCT.

		Adjusted geometric mean		Geometric mean ratio ³	90% CI for ratio ³
		V / H / A ¹ N = 23	V / H ² N = 25		
Valsartan	AUC _{0-τ} (ng.h/mL)	73385.6	66902.5	1.10	0.88 - 1.37
	C _{ssmax} (ng/mL)	9926.6	8595.5	1.15	0.94 - 1.41
HCTZ	AUC _{0-τ} (ng.h/mL)	1868.6	1813.3	1.03	0.86 - 1.24
	C _{ssmax} (ng/mL)	219.3	215.7	1.02	0.86 - 1.20

As seen in **Tables 3(a)-(c)**, with the exception of HCT when co-administered with valsartan (ref), the 90% CIs of the ratio (AUC_{test}/AUC_{ref}) for all individual components lay outside the pre-determined no effect boundary of 70 to 130 %.

Reviewer's comments:

- *The rationale for selecting the no effect boundary of 70 to 130% was not stated.*
- *Although the observed total systemic exposure (AUC) for all three components following administration of the triple combination exceeded that following administration of the dual combination, no serious adverse events were observed in this study.*
- *The observed mean increase of 25 and 22% in valsartan AUC and C_{max}, respectively, is lesser than the reported inter – individual variability (~ 50% CV) in valsartan PK. Further, according to the current valsartan*

label, a two fold increase in plasma valsartan concentrations, as observed in hepatic impaired patients, do not warrant a dose adjustment.

- *The study design used is identical to the pivotal efficacy trial. The efficacy trial was judged to have demonstrated clinical benefit with no major adverse events (MO's MCR presentation).*
- *Although statistically significant PK drug interactions were observed in this study, they are considered to be minor and not of clinical significance.*
- *The study design is not optimal. The study should have been designed to test the triple combination against the individual components, i.e., triple vs. mono as against triple vs. dual.*

4.1.4.6.4 Safety results

Eighteen of the 111 patients enrolled in the study experienced adverse events. A total of 30 AEs were reported, of which the investigators consider 5 AEs (hypokalemia, increased blood glucose, dizziness, increased serum amylase, increased lipase, and atrial fibrillation) to be related to the study drug. One serious adverse event of atrial fibrillation (related to study drug, possible pre-existing undiagnosed condition) was reported in a patient in cohort 4. The patient was withdrawn from the study and transferred to the ICU.

4.1.4.7 Conclusions

There dose not appear to be a clinically significant pharmacokinetic drug interaction between valsartan, hydrochlorothiazide, and amlodipine at steady state when administered together as a triple combination.

4.1.5 Study VEA489A2105 (Relative BA - amlodipine)

An open label, randomized, single-dose, two-way crossover design study to determine the bioavailability of 5 mg amlodipine clinical service form (CSF) capsule relative to that of the 5 mg amlodipine administered as one 5 mg Norvasc® tablet.

Protocol number: VEA489A2105

Investigator: _____

Study site: _____

Study dates: 09/17/2008 to 10/18/2008

b(4)

4.1.5.1 Objectives

The objectives of the study were to determine the bioavailability of an over encapsulated amlodipine 5 mg tablet (CSF) relative to Norvasc 5 mg.

4.1.5.2 Study design

This was a single center, open label, randomized, two period crossover design study. The treatment periods were separated by a washout period of a minimum of 14 days. Each of the subjects was randomized to receive the following:

1. Single oral dose over encapsulated amlodipine 5 mg (Test).
2. Single oral dose of Norvasc 5mg (Reference).

4.1.5.2.1 Study medication

1. Amlodipine 5 mg CSF over encapsulated formulation, Batch No. 15172.2
2. Norvasc® 5 mg, Batch No. 6QL389A

4.1.5.2.2 Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 16h, 24h, 36h, 48h, 72h, 96h, 120h, 144h, and 168h post dose.

4.1.5.2.3 Pharmacokinetic data analysis

Using noncompartmental methods, the following pharmacokinetic measures were determined for all three treatments.

C_{max} , AUC_{last} , AUC_{inf} , T_{max} , λ_z and $t_{1/2}$

4.1.5.2.4 Statistical data analysis

Log transformed pharmacokinetic measures of systemic exposure (C_{max} , AUC) were analyzed using ANOVA linear mixed effects model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect. Point estimates and associated 90 % confidence intervals (CI) were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means.

4.1.5.3 Safety assessments

Physical examination, vital signs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events reported were collected and evaluated.

4.1.5.4 Bioanalytical method

Plasma concentrations of V/H/A were measured simultaneously using a validated HPLC/MS/MS method. The performance measures of the assay are presented in Table 1.

Table 1: Performance measures of amlodipine assay in study VEA489A2105 (Ref: Appendix 16.2.5, DMPK RCVEA489A2105)

Linearity	0.025 to 10 ng/mL (weighted 1/x ² , r > 0.999)
Precision (% CV)	2.8 to 5.4
Accuracy (% Bias)	-0.3 to 3.6

Reviewer's comment:

The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

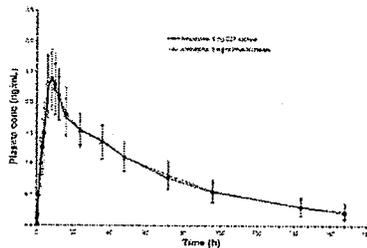
4.1.5.5 Study Results

4.1.5.5.1 Subject demographics

All the 24 subjects enrolled in the study completed both periods of the study. The subject demographics were uniform across treatment groups. The mean (±SD) age and weight were 26.3 years (±7.5 years) and 58.7 Kg (±7.2 Kg), respectively.

4.1.5.5.2 Pharmacokinetic results

Figure 1 presents a graphical comparison of the mean (±SD) plasma concentration versus time profiles for the CSF and Norvasc, along with the relevant pharmacokinetic measures.



PK parameter	Arithmetic mean ± SD (CV%)	
	5 mg CSF capsule	5 mg marketed product
N	24	23
t _{max} (h)**	8.0 (6.0, 10.0)	8.0 (6.0, 10.0)
C _{max} (ng/mL)	2.5 ± 0.45 (18.2)	2.5 ± 0.51 (20.2)
AUC ₀₋₁₂ (ng·hr/mL)	138.4 ± 30.65 (22.1)	141.7 ± 34.13 (24.1)
AUC _{0-∞} (ng·hr/mL)	153.5 ± 38.83 (25.3)	160.9 ± 49.43 (30.7)
t _{1/2} (h)	47.1 ± 16.04 (21.3)	50.5 ± 15.4 (30.5)

Figure 1: Plot of the mean (±SD) plasma concentration versus time for the over encapsulated amlodipine and Norvasc. The triangles represent Norvasc and the circles represent the over encapsulated amlodipine. The relevant pharmacokinetic measures for the individual components are presented in the panel on the right.

4.1.5.5.3 Statistical analysis results

Table 3 presents the results of the statistical analysis of pharmacokinetic exposure measures for over encapsulated amlodipine (CSF) and Norvasc. As seen in **Table 3**, the 90% CI of the ratios for AUC and C_{max} (test/reference) lies within 80 to 125%, and therefore the two formulations do not significantly differ in the extent of exposure.

Table 4: Summary of results of the statistical analysis of PK measures (Ref: Tables 14.2-1.1).

Parameter (Unit)	Adjusted geo-mean*		Estimate	Geo-mean ratio*	
	AML(CSF)	NORVASC		Lower 90% C L	Upper 90% C L
C_{max} (ng/mL)	2	2	0.99	0.93	1.04
AUC (0-last) (hr.ng/mL)	135	138	0.98	0.94	1.02
AUC (0-inf) (hr.ng/mL)	149	154	0.97	0.92	1.02

4.1.5.6 Conclusions

- The rate (C_{max}) and extent (AUC) of absorption of amlodipine following administration of a single dose of over encapsulated amlodipine (CSF) 5 mg is not significantly different from that following administration of a single dose of Norvasc 5 mg.
- The over encapsulated amlodipine 5 mg is bioequivalent to Norvasc 5mg.

5 NEW DRUG APPLICATION FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics				
NEW DRUG APPLICATION FILING AND REVIEW FORM				
<i>General Information About the Submission</i>				
Information		Information		
NDA Number	22314	Brand Name	Exforge HCT [®]	
OCPB Division (I, II, III)	OCPI	Generic Name	Amlodipine/Valsartan/Hydrochlorothiazide	
Medical Division		Drug Class	CCB/ARB/Diuretic	
OCPB Reviewer	Divya Menon-Andersen, Ph.D	Indication(s)	Antihypertensive	
OCPB Team Leader (Acting)	Robert Kumi, Ph.D (Filing)	Dosage Form	Tablet	
	Angelica Dorantes, Ph.D. (CPB)	Dosing Regimen	QD	
Date of Submission	06/30/08	Route of Administration	Oral	
Estimated Due Date of OCPB Review	02/28/09	Sponsor	Novartis	
PDUFA Due Date	04/30/09	Priority Classification	Standard	
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.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
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		PK profiles for each of the components were determined in all groups.
In-vivo effects of primary drug:	X			
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	3	
replicate design; single / multi dose:			
Food-drug interaction studies:			
Dissolution:	X (BE waiver)	1	
(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		5 (in vivo)	
Filability and QBR comments			
	"X" if yes		
Application filable?	X		
Comments sent to firm?	No		
QBR questions (key issues to be considered)			
Other comments or information not included above			
Primary reviewer Signature and Date	Divya Menon-Andersen, 08/18/08		
Secondary reviewer Signature and Date	Robert Kumi, 08/18/2008 (Filing) Angelica Dorantes, 02/27/2009 (CPB)		

CC: NDA 22-314, HFD-110(Nguyen), HFD-860(Dorantes, Uppoor, Mehta),

**6 DIVISION OF SCIENTIFIC INVESTIGATIONS AUDIT REQUEST
MEMORANDUM**

6.1 DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: September 3, 2008
TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48
THROUGH: (Required for international inspections)
Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular
and
Renal Products, HFD-110
FROM: Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, Division
of Cardiovascular and Renal Products, HFD-110
SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-314
Exforge HCT (amlodipine besylate USP, valsartan USP,
hydrochlorothiazide USP) Tablets

6.1.1 Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
VEA489A 2305		

b(4)

6.1.2 International Inspections:

6.1.3 (Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

6.1.4

6.1.5 We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

- The results of the bioequivalence (BE) study conducted at the site identified for inspection are important in linking the observed results from the pivotal clinical study to the to-be-marketed (TBM) dosage form, and also in granting BE waivers for two other TBM strengths.
- The bioanalytical work for the BE study was performed in China.

6.1.6 Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **February 1, 2009**. We intend to issue an action letter on this application by **April 30, 2009**.

Should you require any additional information, please contact Quynh Nguyen, RPM, (301) 796-0510.

Concurrence: (Optional)

Divya Menon-Andersen, Ph.D., Clinical Pharmacology Reviewer 08/22/08

Robert Kumi, Ph.D., Clinical Pharmacology Team Leader (Acting) 08/22/08

Norman Stockbridge, M.D., Ph.D., Division Director 09/03/08

6.2 DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: December 02, 2008

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

THROUGH: (Required for international inspections)
Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular
and
Renal Products, HFD-110

FROM: Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, Division
of Cardiovascular and Renal Products, HFD-110

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-314
Exforge HCT (amlodipine besylate USP, valsartan USP,
hydrochlorothiazide USP) Tablets

6.2.1 Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
VEA489A 2306		

b(4)

6.2.2 International Inspections:

6.2.3 (Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

6.2.4

6.2.5 We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

- The results of the bioequivalence (BE) study conducted at the site identified for inspection are important in linking the observed results from the pivotal clinical study to the to-be-marketed (TBM) dosage form.
- The bioanalytical work for the BE study was performed in China.

6.2.6 Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **February 1, 2009**. We intend to issue an action letter on this application by **April 30, 2009**.

Should you require any additional information, please contact Quynh Nguyen, RPM, (301) 796-0510.

Concurrence: (Optional)

Divya Menon-Andersen, Ph.D., Clinical Pharmacology Reviewer

Angelica Dorantes, Ph.D., Clinical Pharmacology Team Leader (Acting)

Norman Stockbridge, M.D., Ph.D., Division Director

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

/s/

Divya Menon-Andersen
2/27/2009 02:22:38 PM
BIOPHARMACEUTICS

Angelica Dorantes
2/27/2009 02:54:01 PM
BIOPHARMACEUTICS

ONDQA (Biopharmaceutics) Review

NDA: 22-314
Submission Date: 03/30/09
Product: Exforge HCT® (amlodipine besylate USP, valsartan USP, hydrochlorothiazide USP) Combination Tablets
Type of Submission: Response to Questions on Original NDA
Sponsor: Novartis
Reviewer: Tapash K. Ghosh, Ph.D.

Background: In response to the following question, the sponsor submitted their response which has been reviewed in this document:

Q. Submit individual tablet dissolution data used to generate plots for Figure 12-1 and Figure 12-2 provided in your response to Question 12 of the Amendment dated March 6, 2009.

The sponsor's response is as follows:

At this time, Novartis would like to acknowledge that the original plots provided in the response dated March 3, 2009 inadvertently contained values for the amlodipine dissolution packaged in — blisters. The — blisters are specifically for Zones 3 and 4 in the "Rest of World" countries and not meant for the USA. Novartis discovered this error when tabulating the data requested for the FDA. Novartis apologizes for this oversight on our part and for any inconvenience this may have caused. Please note that this caused only a slight change in the range of dissolution data. The mean values for the dissolution data have not been affected by the exclusion of the — blisters.

b(4)

b(4)

The grand mean for all 5/160/12.5, 10/160/12.5, 5/160/25 and 10/160/25 mg batches tested at release and stability range from — at 30 minutes. Novartis will agree to the Agency's proposal for a Q = — specification for the 5/160/12.5, 10/160/12.5, 5/160/25 and 10/160/25mg strengths. However, the specification time must be increased from 30 to 45 minutes to allow for normal laboratory variability. Similarly, the grand mean for all 10/320/25mg batches tested on release and stability is — which is very close to the Agency's proposal of Q = — in 30 minutes. As a result, Novartis proposes a Q-value of — in 45 minutes for the 10/320/25mg strength.

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b(4)

Reference is made to the updated box plots provided in Figure 2-1 and Figure 2-2 which show the amlodipine besylate dissolution mean values for each strength of VEA489 tablets at 30 minutes and 45 minutes, respectively. The box represents the 25th to 75th percentiles, + is the mean, the interior box is the median and the lines extend to the range of the data. The data show that Q = — for 5/160/12.5, 10/160/12.5, 5/160/25 and 10/160/25mg and Q = — for 10/320/25mg is not appropriate at 30 minutes. Hence our proposal for the 45 minute testing point.

b(4)

Figure 2-1 VEA489 tablet dissolution at 30 minutes



b(4)

Figure 2-2 VEA489 tablet dissolution at 45 minutes



b(4)

Recommendation: Based on the updated box plots provided in Figure 2-1 and Figure 2-2 which show the amlodipine besylate dissolution mean values for each strength of VEA489 tablets at 30 minutes and 45 minutes, respectively and after reviewing the raw data submitted by the sponsor, the Agency does not accept the sponsor's proposal of Q = @ 45 minutes for 160/12/5/5, 160/12.5/10, 160/25/5, 160/25/10 mg strengths and Q

b(4)

@ 45 minutes for 320/25/10 mg strength for amlodipine. However, the Agency recommends Q= — @ 30 minutes for **amlodipine** in all strengths as data on no batch submitted by the sponsor failed to adhere to this specification. Therefore, the revised recommended dissolution methodology and specifications are as follows:

b(4)

Dosage Strengths (mg) (Valsartan/HCTZ/amlodipine)	160/12/5/5, 160/12.5/10, 160/25/5, 160/25/10	320/25/10
Dissolution Medium	pH 6.8 phosphate buffer (USP)	pH 6.8 phosphate buffer (USP)
Volume	900 mL	pH 6.8 phosphate buffer
Apparatus	USP II (Paddle)	USP II (Paddle)
Speed	50 rpm	55 rpm
Q-time	30 min	30 min
Q-values for		
	Valsartan	
	HCTZ	
	amlodipine	

b(4)

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

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

/s/

Tapash Ghosh
4/7/2009 11:30:44 AM
BIOPHARMACEUTICS

Patrick Marroum
4/7/2009 11:46:48 AM
BIOPHARMACEUTICS

ONDQA (Biopharmaceutics) Review

NDA: 22-314
Submission Date: 06/30/08
Product: Exforge HCT[®] (amlodipine besylate USP, valsartan USP, hydrochlorothiazide USP) Combination Tablets
Type of Submission: Original NDA
Sponsor: Novartis
Reviewer: Tapash K. Ghosh, Ph.D.

Background: In this new drug application, Novartis is filing for the registration of valsartan/ hydrochlorothiazide (HCTZ)/amlodipine fixed combination tablets (referred here as VEA 489 with the proposed brand name of Exforge HCT[®]) for the following five dose strengths: 160/12.5/5 mg, 160/12.5/10 mg, 160/25/5 mg, 160/25/10 mg and 320/25/10 mg. The objectives of the formulation development were to generate an immediate release tablet combination product that was bioequivalent to the clinical free forms of Diovan (valsartan) commercial tablets, hydrochlorothiazide clinical service form (CSF) capsules and amlodipine CSF capsules (Norvasc over-encapsulated tablet with backfill).

The registration of the product is based on the following development program: 1) a phase III clinical study to demonstrate the efficacy and safety of the triple combination; 2) the biopharmaceutics development program to demonstrate bioequivalence between the fixed triple combination of the final market image (FMI) tablet and the free combination of corresponding doses of the clinical service formulations (CSFs) used in the phase III clinical study; 3) a pharmacokinetic interaction study; and 4) a food effect bioavailability study with the FMI tablet.

In this document, the *in vitro* data supporting the biowaiver request have been reviewed and minor modifications on the sponsor's proposed dissolution specifications for amlodipine have been recommended.

Recommendation: Based on the dissolution profiles, f2 values, compositional proportionality and the sponsor's rationale, biowaiver for VEA489 160/25/5 mg, 160/12.5/10 mg and 320/25/10 mg film-coated tablets can be granted provided the Office of Clinical Pharmacology confirms the results of the BE studies VEA489A 2305 and VEA489A 2306.

Also, based on the results of dissolution studies (average and %RSD), the Agency recommended dissolution testing methodology and specifications are as follows:

Dosage Strengths (mg) (Valsartan/HCTZ/amlodipine)	160/12/5/5, 160/12.5/10, 160/25/5, 160/25/10	320/25/10
Dissolution Medium	pH 6.8 phosphate buffer (USP)	pH 6.8 phosphate buffer (USP)
Volume	900 mL	pH 6.8 phosphate buffer
Apparatus	USP II (Paddle)	USP II (Paddle)
Speed	50 rpm	55 rpm
Q-time	30 min	30 min
Q-values for		
	Valsartan	
	HCTZ	
	amlodipine	

b(4)

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. _____

Formulation Development History:

Two variants were developed for 160/12.5/5 mg and 160/25/10 mg strengths: variant .001 with _____ and variant .002 with _____ (refer to Table 2-1). Different _____ were used to produce different acceptable valsartan *in-vitro* release in multiple media. One variant (variant .003; refer to Table 2-1) was developed for 160/12.5/5 mg strength to increase the likelihood of demonstrating Bioequivalence.

b(4)

Table 2-1 Composition of VEA489 tablet formulations during development (mg/tablet)

Component	5/160/12.5 mg 6001954.001	5/160/12.5 mg 6001954.002	5/160/12.5 mg 6001954.003	10/160/25 mg 6001955.001	10/160/25 mg 6001955.002	10/320/25 mg 6002196.002
Tablet core layer						
Valsartan						
Hydrochlorothiazide						
Amlodipine besylate						
Microcrystalline cellulose						
Hydroxypropyl cellulose Low-subst.						
Sodium starch glycolate						
Iron oxide, yellow						
Croscopolidone						
Magnesium stearate						
Colloidal silicon dioxide						
Coating						
Basic coating premix - Yellow						
Basic coating premix - White						
Basic coating premix - Red						
Water						
Total film-coated tablet weight						

b(4)

Two clinical studies (VEA489A2305 and VEA489A2306) were conducted for the following VEA489 strengths: 160/12.5/5 mg with _____ variants .001 and .002 and _____ variant .003, and 160/25/10 mg with _____ variants .001 and .002, respectively. As reported by the sponsor, Table 2-2 and Table 2-3 list the BE study results for 160/12.5/5 mg and 160/25/10 mg strengths, respectively (*Refer to clinical pharmacology review for detail review*).

b(4)

_____ variant .001 at strengths 160/12.5/5 mg and 160/25 /10 mg demonstrated bioequivalence for all three active components in clinical studies VEA489A2305 and VEA489A2306. The variant was selected as the final market image (FMI) over other the two variants based on the results that the ratios of geometric means of PK parameters for all three components were close to 1.0.

b(4)

1 Page(s) Withheld

 x Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

COMPARATIVE DISSOLUTION FOR BIOWAIVERS

No BE or BA studies have been performed for VEA489 160/25/5 mg, 160/12.5/10 mg and 320/25/10 mg film-coated tablets as Novartis requested a biowaiver for these strengths.

Comparative dissolution profiles for valsartan, hydrochlorothiazide (HCT) and amlodipine besylate drug substances were obtained on VEA489 film-coated tablets in three different media, pH 6.8 (phosphate buffer), pH 4.5 (acetate buffer) and pH 1.0 (0.1N HCl). The dissolution tests were performed using USP apparatus 2 (paddle) at 50 rpm for the 160/12.5/5, 160/12.5/10, 160/25/5 and 160/25/10 mg tablets. Dissolution for the 320/25/10 mg strength tablet was performed using USP apparatus 2 (paddle) at 50 rpm and at 55 rpm. Testing at 55 rpm for the 320/25/10 mg tablets was required to overcome cone formation associated with the higher tablet weight — for the 10/320/25 mg tablets vs — for the lower strength tablets).

b(4)

Dissolution profiles and f2 similarity factors were calculated for each combination of tablets tested and the results of the similarity factors are presented in the following section.

Dissolution Method for Release and Stability

The final dissolution conditions and specifications for release and stability testing are as outlined in Table 2-9.

Amlodipine and hydrochlorothiazide (HCT) are soluble in physiologically relevant pHs (1 to 7.5). However, valsartan has a pH dependent solubility (insoluble in acidic pHs and highly soluble at pHs above 5.5). At pH 6.8, however, amlodipine, valsartan, and hydrochlorothiazide (HCT) have acceptable solubility and sink conditions in 900 ml. Therefore, the recommended dissolution medium for VEA489 FCTs is pH 6.8 phosphate buffer.

USP apparatus 2 (paddle) was selected for dissolution testing because the dosage form is a tablet. A paddle speed of 50 RPM was selected for all strengths except the highest dosage strength (10/320/25 mg), as this will have the highest likelihood of discrimination and this speed is also consistent with the speed employed in the biowaiver guidance. The increase in paddle speed from 50 to 55 RPM has been introduced to minimize cone formation associated with the higher tablet weight of the VEA489 10/320/25 mg — for the 10/320/25 mg tablets vs — for the lower strength tablets). It has been confirmed that results obtained at 55 RPM for the highest dosage strength are comparable to the results obtained at 50 RPM for the lower dosage strengths of VEA489 film-coated tablets. Both paddle speeds with USP vessel provided adequate discrimination for drug product in terms of packaging and storage conditions.

b(4)

Table 2-9 Proposed dissolution method conditions and specifications for VEA489 FCTs

Dosage strengths	5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg and 10/160/25 mg	10/320/25 mg
Volume of dissolution medium	900 milliliters	900 milliliters
Dissolution medium	pH 6.8 phosphate buffer (USP)	pH 6.8 phosphate buffer (USP)
Apparatus	Paddle	Paddle
Speed	50 RPM	55 RPM
Q-time	30 minutes	30 minutes
Q-value	Valsartan Q= HCT Q= Amlodipine Q=	Valsartan Q= HCT Q= Amlodipine Q=

b(4)

Products tested

Five dosages of VEA489 were tested. The batch numbers were given in the following table:

<u>Product strength (mg)</u>	<u>Batch number</u>
160/12.5/5	AEUS/2005-0369 (Pilot)
160/12.5/10	H398FD (Pivotal)
160/25/5	H399FD (Pivotal)
160/25/10	AEUS/2006-0002 (Pilot)
320/25/10	AEUS/2006-0365 (Pilot)

Discriminating power /Bio-relevance of the Dissolution Method

During development of VEA489 FCTs, three different formulations were investigated: a) _____ (current FMI) _____

b(4)

Novartis manufactured one batch (5/160/12.5 mg dosage strength) of each of these three formulations and one batch (10/160/25 mg dosage strength) of each of the first two formulations (current FMI and _____). Dissolution results comparing the three formulations are presented in Figure 2-5, Figure 2-6, and Figure 2-7 for amlodipine, valsartan and HCT, respectively.

b(4)

The three formulations were administered to healthy volunteers during the pilot BA program (later agreed by the FDA as pivotal BE study). Three different formulations of VEA489 FCTs were compared against clinical service forms (CSF) formulations of individual actives (respective innovator products for valsartan, HCTZ and amlodipine).

All three formulations for the 5/160/12.5 mg dosage strength were found to be bio-equivalent to the amlodipine and HCTZ reference products (in the same subjects) (Table 2-2) and the rate of dissolution using the proposed method is different between the — and the other two formulations (current FMI and — formulations) for amlodipine, and HCTZ (refer to Figure 2-5, and Figure 2-7, respectively). Thus, *in-vitro* dissolution method is able to discriminate between different formulations based on different rate of dissolution of HCTZ and amlodipine and does not correlate with *in-vivo* exposures.

b(4)

For valsatran, the rate of dissolution using the proposed method could not discriminate between the — and the other two formulations (current FMI and — formulations). However, the dissolution profiles were discriminatory between the current FMI (prototype I) and the reference valsatran product. Also only the current FMI (prototype I) was strictly bioequivalent to the reference valsatran product (Table 2-2). Thus, *in-vitro* dissolution of valsatran might be able to discriminate between differences in *in-vivo* release rates.

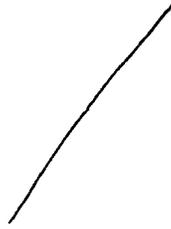
b(4)

Figure 2-5 Dissolution of Amlodipine from different formulations



b(4)

Figure 2-7 Dissolution of HCT from different formulations



b(4)

Comparison and Analysis of Results Across Studies

I. Bio-waiver request for the 160/25/5 mg valsartan/HCTZ/amlodipine dose

The bio-waiver for the 160/25/5 mg valsartan/HCTZ/amlodipine fixed combination FMI tablet is requested by the sponsor based on the rationale below:

- The manufacturing process of the 160/25/5 mg valsartan/HCTZ/amlodipine formulation is identical to that of the Prototype I of 160/25/10 mg fixed combination tablet, for which the bioequivalence was established [Study VEA489A2306].
- The qualitative composition of 160/25/5 mg valsartan/HCTZ/amlodipine formulation is identical to that of the Prototype I of 160/25/10 mg fixed combination tablet for which the bioequivalence was established [Study VEA489A2306].
- The quantitative composition is also similar. The 160/25/5 formulation is obtained by replacing _____ in the 160/25/10 mg formulation. The total difference of _____ between the 5 mg and 10 mg formulations is _____ which is negligible, and would have no impact on the performance of the product.
- Valsartan, HCTZ and amlodipine exhibit linear and dose proportional pharmacokinetic.
- In vitro dissolution of valsartan, HCT and amlodipine is similar in three pH media between the 10/160/25 mg and 5/160/25 mg fixed combination products.

b(4)

Dissolution testing between 160/25/10 mg (reference) and 160/25/5 mg (test) fixed combination products

Dissolution of VEA489 FCT tablets were tested under various pHs using USP II (paddle) at 50 rpm in 900ml dissolution media. The batches used for the comparative study are AEUS/2006-0002 (160/25/10mg, pilot scale, reference batch) and H399FD (160/25/5, production scale, test batch). The data and figures in pH 6.8 are presented below.

Table 3-15 VEA489 tablets, batch #H399FD: 160/25/5mg, 900 ml pH 6.8 phosphate buffer, 50 rpm paddles

No.	Valsartan			Hydrochlorothiazide			Amlodipine		
	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.
Avg.	86	89	91	83	88	89	73	80	82
%RSD	2.06	1.71	1.57	2.00	1.68	1.53	2.15	1.78	1.51

b(4)

Table 3-16 VEA489 tablets, batch #AEUS/2006-0002: 160/25/10 mg, 900 ml pH 6.8 phosphate buffer, 50 rpm paddles

No.	Valsartan				Hydrochlorothiazide				Amlodipine			
	10 min.	20 min.	30 min.	Rapid stir*	10 min.	20 min.	30 min.	Rapid stir*	10 min.	20 min.	30 min.	Rapid stir*
Avg.	90	93	94	97	90	94	95	99	75	84	88	94
%RSD	3.60	2.71	2.44	0.78	4.12	2.86	2.59	0.77	5.65	3.93	3.23	1.09

b(4)

Dissolution profiles of valsartan: valsartan/HCTZ/amlodipine 160/25/5 mg (Batch # H399FD) fixed combination tablet (FMI) versus the 160/25/10 mg (Batch# AEUS/2006-0002) fixed combination tablet (FMI) in phosphate buffer pH 6.8 (n = 12)

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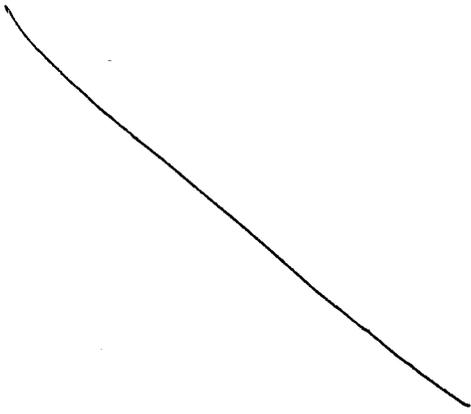
 X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Dissolution profiles of amlodipine: valsartan/HCTZ/amlodipine 160/25/5 mg (Batch # H399FD) fixed combination tablet (FMI) versus the 160/25/10 mg (Batch# AEUS/2006-0002) fixed combination tablet (FMI) in phosphate buffer pH 6.8 (n = 12)



b(4)

f2 similarity factors comparing dissolution profiles of 160/25/5 mg and 160/25/10 mg valsartan/HCTZ/amlodipine fixed combination tablets

Media	160/25/5 mg tablet vs. 160/25/10 mg tablet		
	Valsartan	HCTZ	Amlodipine
900 ml of			
pH 6.8 (phosphate)			
pH 4.5 (acetate)			
pH 1.0 (0.1 N HCl)			

b(4)

Comments: Based on the the composition similarity of the 160/25/5 mg valsartan/HCTZ/amlodipine and 160/25/10 mg valsartan/HCTZ/amlodipine prototype I, the same manufacturing processes for these tablets, and the acceptable in vitro dissolution results, waiver of a bioequivalence study for 160/25/5 mg strength can be granted provided the Office of Clinical Pharmacology review confirms the results of the BE Study VEA489A 2306.

II. Bio-waiver request for the 160/12.5/10 mg valsartan/HCTZ/amlodipine dose

The bio-waiver for the 160/12.5/10 mg valsartan/HCTZ/amlodipine fixed combination FMI tablet is requested based on the rationale below:

- The manufacturing processes of 160/12.5/10 mg valsartan/HCTZ/amlodipine formulation are identical to that of the Prototype I 160/12.5/5 mg fixed combination tablet, for which the bioequivalence was established [CVEA489A2305].
- The qualitative composition of 160/12.5/10 mg valsartan/HCTZ/amlodipine formulation are identical to that of the Prototype I 160/12.5/5 mg fixed combination tablet. for which the bioequivalence was established [CVEA489A2305].
- The quantitative composition is also similar. The 160/12.5/10 formulation is obtained by replacing _____ in the 160/12.5/5 mg formulation. The total difference of _____ between the two formulations is _____ which is negligible, and would have no impact on the performance of the product.
- Valsartan, HCTZ and amlodipine exhibit linear and dose proportional pharmacokinetics.
- *In vitro* dissolution of valsartan, HCT and amlodipine is similar in three pH media between the 10/160/12.5 mg and 5/160/12.5 mg fixed combination products.

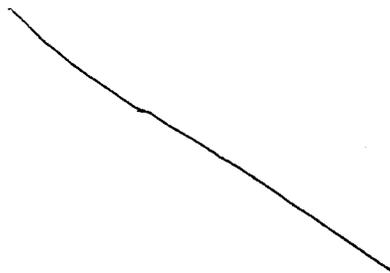
b(4)

Dissolution testing between 160/12.5/5 mg (reference) and 160/12.5/10 mg (test) fixed combination products

Dissolution of VEA489 FCT tablets were tested under various pHs using USP II (paddle) at 50 rpm in 900ml dissolution media, as per the FDA guidance. The batches used for the comparative study are AEUS/2005-0369 (160/12.5/5mg, pilot scale, reference batch) and H398FD (160/12.5/10mg, production scale, test batch). The data at pH 6.8 and f2 values are presented below.

Table 3-13 VEA489 tablets, batch #AEUS/2005-0369: 160/12.5/5 mg, 900 ml pH 6.8 phosphate buffer, 50 rpm paddles

No.	Valsartan				Hydrochlorothiazide				Amlodipine			
	10 min.	20 min.	30 min.	Rapid stir*	10 min.	20 min.	30 min.	Rapid stir*	10 min.	20 min.	30 min.	Rapid stir*



b(4)

Avg.	91	93	94	98	93	96	97	101	79	87	90	96
%RSD	3.24	2.38	2.03	0.90	3.36	2.47	2.06	0.96	5.43	3.53	2.89	1.09

Table 3-14 VEA489 tablets, batch # H398FD: 160/12.5/10 mg, 900 ml pH 6.8 phosphate buffer, 50 rpm paddles

No.	Valsartan			Hydrochlorothiazide			Amlodipine		
	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.
Avg.	88	91	92	86	91	93	72	81	84
%RSD	2.23	1.93	1.94	2.20	1.92	1.90	2.14	1.88	1.70

b(4)

f2 similarity factors comparing dissolution profiles of 160/12.5/10 mg and 160/12.5/5 mg valsartan/HCTZ/amlodipine fixed combination

Media	160/12.5/10 mg tablet vs. 160/12.5/5 mg tablet		
900 ml of	Valsartan	HCTZ	Amlodipine
pH 1.0 (0.1 N HCl)			
pH 4.5 (acetate)			
pH 6.8 (phosphate)			

b(4)

Comments: The composition similarity of the 160/12.5/10 mg valsartan/HCTZ/amlodipine and 160/12.5/5 mg valsartan/HCTZ/amlodipine prototype I, the same manufacturing processes for these tablets, the pharmacokinetic characteristics of valsartan, HCTZ and amlodipine, and the acceptable in vitro dissolution results fulfill the requirements for waiver of a bioequivalence study at 160/12.5/10 mg strength.

Comments: Based on the composition similarity of the 160/12.5/5 mg valsartan/HCTZ/amlodipine and 160/12.5/10 mg valsartan/HCTZ/amlodipine prototype I, the same manufacturing processes for these tablets, and the acceptable in vitro dissolution results, waiver of a bioequivalence study for 160/12.5/10 mg strength can be granted provided the Office of Clinical Pharmacology review confirms the results of the BE Study VEA489A 2305.

III. Bio-waiver request for the 320/25/10 mg valsartan/HCTZ/amlodipine dose

The bio-waiver for the 320/25/10 mg valsartan/HCTZ/amlodipine fixed combination FMI tablet is requested based on the rationale below.

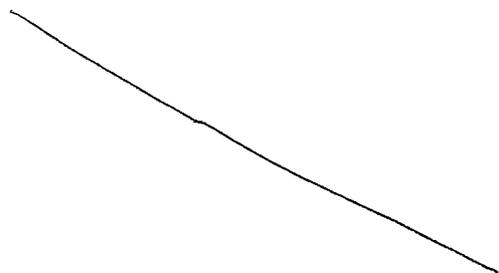
- The manufacturing process of 320/25/10 mg valsartan/HCTZ/amlodipine fixed combination FMI tablet is identical to that of the 160/12.5/5 mg fixed combination prototype I tablet, for which the bioequivalence was established [CVEA489A2305].
- The composition of 320/25/10 mg valsartan/HCTZ/amlodipine fixed combination FMI tablet is proportional in its active and inactive ingredients to the 160/12.5/5 mg valsartan/HCTZ/amlodipine fixed combination prototype I tablet.
- Valsartan, HCTZ and amlodipine exhibit linear and dose proportional pharmacokinetics.
- *In vitro* dissolution for the 320/25/10 mg valsartan/HCTZ/amlodipine was tested under two dissolution method conditions, with paddle speeds of 50 and 55 rpm, respectively. The increase in paddle speed from 50 to 55 rpm is to minimize cone formation associated with the higher tablet weight of 320/25/10 valsartan/HCTZ/amlodipine.

Dissolution testing between 160/12.5/5 mg (reference) and 320/25/10 mg (test) fixed combination products

Dissolution of VEA489 FCT tablets were tested under various pHs using USP II (paddle) at 50 rpm in 900ml dissolution media, as per the FDA guidance. The batches used for the comparative study are AEUS/2005-0369 (160/12.5/5mg, pilot scale, reference batch) and AEUS/2006-0365 (320/25/10, pilot scale, test batch). The dissolution data and f2 values are presented below.

Table 3-17 VEA489 tablets, batch #AEUS/2006-0365: 320/25/10 mg, 900 ml pH 6.8 phosphate buffer, 50 rpm paddles

No.	Valsartan			Hydrochlorothiazide			Amlodipine		
	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.	10 min.	20 min.	30 min.



Avg.	76	82	85	82	86	89	70	77	81
%RSD	7.67	5.03	4.55	1.51	1.10	1.31	2.46	1.75	1.84

b(4)

Table 3-23 VEA489 tablets, batch #AEUS/2005-0365: 320/25/10 mg, 900 ml pH 6.8 phosphate buffer, 55 rpm paddles

No.	Valsartan				Hydrochlorothiazide				Amlodipine			
	10 min.	20 min.	30 min.	45 min.	10 min.	20 min.	30 min.	Rapid stir*	10 min.	20 min.	30 min.	45 min.

b(4)

Avg.	91	92	93	94	90	92	93	95	80	86	87	87
%RSD	1.75	1.33	1.25	1.28	89	91	92	94	2.12	1.44	0.91	1.96

Table 3-24 VEA489 tablets, batch #AEUS/2005-0369: 160/12.5/5 mg (2 tablets per vessel), 900 ml pH 6.8 phosphate buffer, 55 rpm paddles

No.	Valsartan				Hydrochlorothiazide				Amlodipine			
	10 min.	20 min.	30 min.	45 min.	10 min.	20 min.	30 min.	Rapid stir*	10 min.	20 min.	30 min.	45 min.

b(4)

Avg.	88	89	90	91	88	90	91	92	76	85	87	84
%RSD	0.92	0.86	0.85	0.72	0.95	0.88	0.81	0.63	1.13	1.64	2.01	0.95

f2 similarity factors comparing dissolution profiles of 320/25/10 mg and 160/12.5/5 mg valsartan/HCTZ/amlodipine fixed combination tablets

Media	320/25/10 mg tablet vs. 160/12.5/5 mg tablet		
	Valsartan	900 ml of	Valsartan
Rotation 50 RPM, 900 ml of			
pH 1.0 (0.1 N HCl)			
pH 4.5 (acetate)			
pH 6.8 (phosphate)			
Rotation 55 RPM, 900 ml of			

b(4)

pH 1.0 (0.1 N HCl)				
pH 4.5 (acetate)				
pH 6.8 (phosphate)				

b(4)

Comments: Based on the composition proportionality of the 320/25/10 mg valsartan/HCTZ/amlodipine and 160/12.5/5 mg amlodipine/valsartan/HCTZ prototype I, the same manufacturing processes for these tablets, and the acceptable *in vitro dissolution results*, waiver of a bioequivalence study for 320/25/10 mg strength can be granted provided the Office of Clinical Pharmacology review confirms the results of the BE Study VEA489A 2305.

Q-value and Q – time

Based on the results of dissolution studies (average and %RSD), the Agency recommendations are as follows:

Dosage Strengths (mg) (Valsartan/HCTZ/amlodipine)	160/12/5/5, 160/12.5/10, 160/25/5, 160/25/10	320/25/10
Dissolution Medium	pH 6.8 phosphate buffer (USP)	pH 6.8 phosphate buffer (USP)
Volume	900 mL	pH 6.8 phosphate buffer
Apparatus	USP II (Paddle)	USP II (Paddle)
Speed	50 rpm	55 rpm
Q-time	30 min	30 min
Q-values for		
	Valsartan	
	HCTZ	
	amlodipine	

b(4)

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