CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-818

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

JAN 14 1998

CLINICAL PHARMACOLOGY/BIOPHARMACEUTIC REVIEW

NDA: 20-818 (Amendment BB & BC) **SUBMISSION DATE:** DECEMBER 12, 1997
Diovan HTC™ (Valsartan & Hydrochlorothiazide) DECEMBER ~~12~~ 23, 1997
Tablets (160/12.5 and 80/12.5 mg)

NOVARTIS PHARMACEUTICALS **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA AMENDMENT

BACKGROUND:
Diovan™ (Valsartan) is a synthetic angiotensin II receptor antagonist recently approved (NDA 20-665) for the treatment of hypertension. The biopharmaceutics review of the sponsor's submission for a combination tablet containing valsartan 160 mg and hydrochlorothiazide (HCTZ) 12.5 mg and valsartan 80 mg and HCTZ 12.5 mg was completed on 10/30/97. The sponsor's response to the comment on dissolution specification was reviewed on and a telecon was held with the sponsor on December 5, 1997 during which the sponsor was requested to submit individual dissolution data from the one year stability sample dissolution profiles summarized in their November 7, 1997 submission. These submissions are follow-up to the telecon.

COMMENTS

The individual dissolution data from the one year stability sample dissolution profiles did not justify a change of the interim dissolution specification. The sponsor was informed about this by the Project Manager (Kathleen Bongiovanni) and the sponsor now agrees to the interim dissolution specification of Q= at 30 min for valsartan and HCTZ pending the submission of the two and the three year stability data.

CONCLUSION:
The Division of Pharmaceutical Evaluation I has completed the review of the sponsor's responses to the Agency's comments and observes that the sponsor now agrees to the interim dissolution specification of Q= at 30 min for valsartan and HCTZ.

1/13/98
Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. ————

cc: NDA 20-818, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy), ~~HFD-340~~

NOV 24 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTIC REVIEW

NDA: 20-818 (Amendment BZ) SUBMISSION DATE: NOVEMBER 7, 1997
Diovan HTC™ (Valsartan & Hydrochlorothiazide)
Tablets (160/12.5 and 80/12.5 mg)

NOVARTIS PHARMACEUTICALS REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA AMENDMENT

BACKGROUND:

Diovan™ (Valsartan) is a synthetic angiotensin II receptor antagonist recently approved (NDA 20-665) for the treatment of hypertension. The biopharmaceutics review of the sponsor's submission for a combination tablet containing valsartan 160 mg and hydrochlorothiazide (HCTZ) 12.5 mg and valsartan 80 mg and HCTZ 12.5 mg was completed on 10/30/97 and the present submission addresses the comments that were sent to the sponsor.

COMMENTS SENT TO THE FIRM AND RESPONSES:

Comment 1. The sponsor is requested to submit full dissolution profiles (sampling times at 10, 15, 30, and 45 minutes) for 1 and 2 year stability samples for both components of the formulations.

Comment 2. INTERIM DISSOLUTION SPECIFICATION: Based on the dissolution data submitted by the sponsor, the interim dissolution specifications (pending the response to request 1 above) should be:
Q= at 30 min for valsartan and HCTZ

RESPONSES: The sponsor has submitted dissolution profiles (sampling times at 10, 30 and 45 minutes) for 80/12.5 mg and 160/12.5 mg tablets at 0-time and after 1 year storage at 30°C/60% RH (attached). The sponsor claims that no difference would be expected between the 15 minute and 20 minute sample and commits to perform dissolution profiles on the 2-year stability samples.
The sponsor agrees to a Q of in 30 minutes for valsartan but recommends a Q of in 30 minutes for hydrochlorothiazide (HCTZ). The sponsor argued that the slight decrease in HCTZ dissolution rata might be due to dissolution cone effect since the formulation contains insoluble excipients (such as microcrystalline cellulose) . Variability, including decrease in dissolution, could arise as a result of a cone, which is affected by the sampling procedure, the sampling probe and small variations in hydrodynamics in the vessel.

AGENCY COMMENTS TO BE SENT TO THE SPONSOR:

1. Based on the additional data submitted by the sponsor, a change in the interim specifation could not be recommended. Therefore the interim dissolution specifications (pending the availability of the 2-year dissolution) should still be:
Q= at 30 min for valsartan and HCTZ

2.The sponsor is requested to submit full dissolution profiles (sampling times at 10, 15, 30, and 45 minutes) for 2 year stability samples for both components of the formulations. These data will be used to finalize the dissolution specifications for both components of the formulation.

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has completed the review of the sponsor's responses to the Agency's comments and recommends that comments 1 and 2 above should be sent to the sponsor.

11/24/97

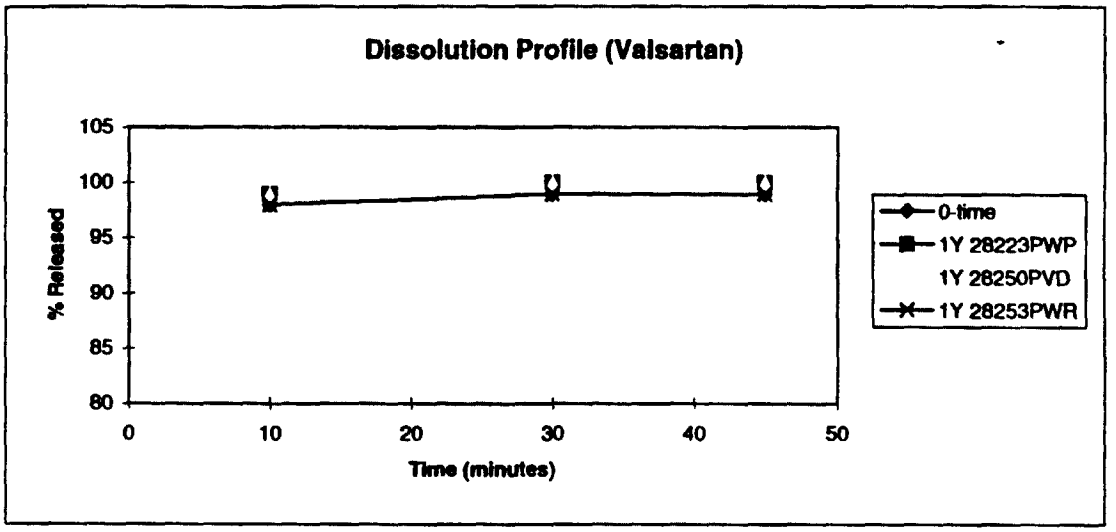
Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. ———— 11/24/97

cc: NDA 20-818, HFD-110, HFD-860 (Fadiran), Bob Walters (HFD-110), CDR (Attn: Barbara Murphy), HFD-340 (Vish).

Figure 1. **Dissolution Profile on Valsartan/HCT 80/12.5mg**
Lot# 17/249/1 stored @ 30C/60% RH

Time (min.)	% Released (Valsartan)			
	(0-Time)	(1Y 28223)	(1Y 28250)	(1Y 28253)
10	98	99	99	98
30	99	100	100	99
45	99	100	100	99



Time (min.)	% Released (HCT)			
	(0-Time)	(1Y 28223)	(1Y 28250)	(1Y 28253)
10	97	95	94	93
30	97	96	95	94
45	97	96	95	93

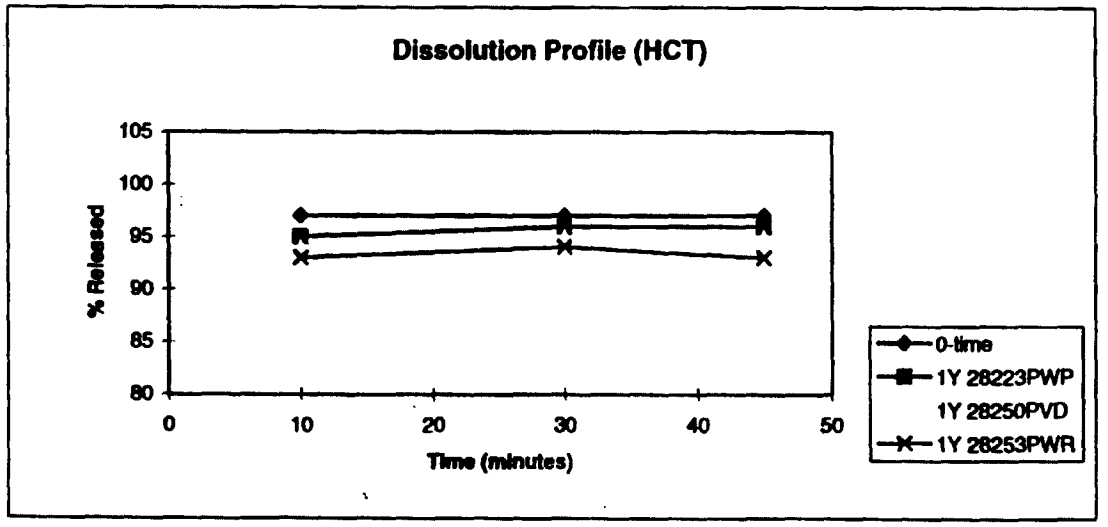
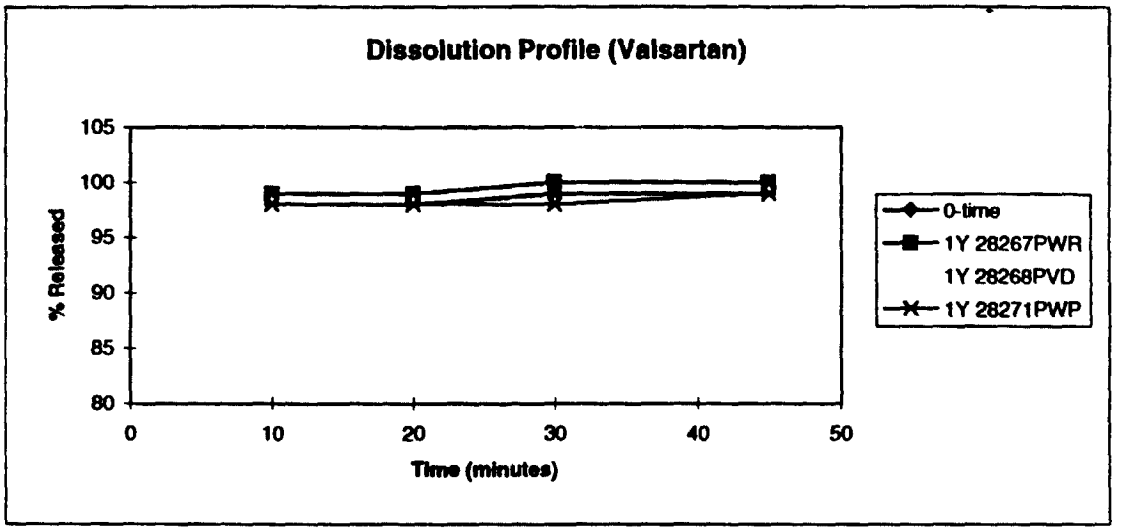


Figure 2. **Dissolution Profile on Valsartan/HCT 160/12.5mg**
Lot# 17/250/1 stored @ 30C/60% RH

Time (min.)	% Released (Valsartan)			
	(0-Time)	(1Y 28267)	(1Y 28268)	(1Y 28271)
10	98	99	98	98
20	98	99	98	98
30	99	100	98	98
45	99	100	99	99



Time (min.)	% Released (HCT)			
	(0-Time)	(1Y 28267)	(1Y 28268)	(1Y 28271)
10	97	95	95	96
20	98	95	96	97
30	98	96	97	97
45	99	96	97	98

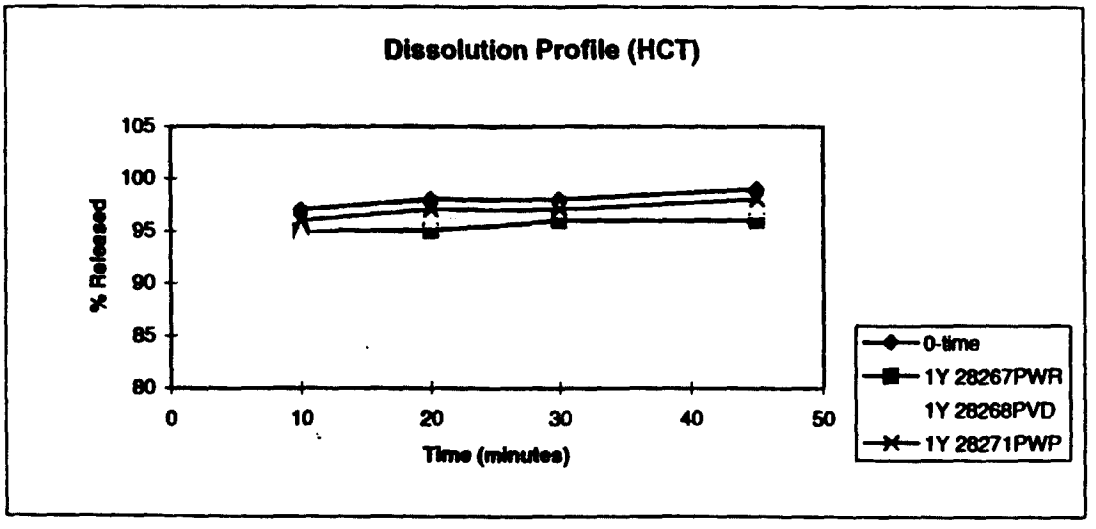
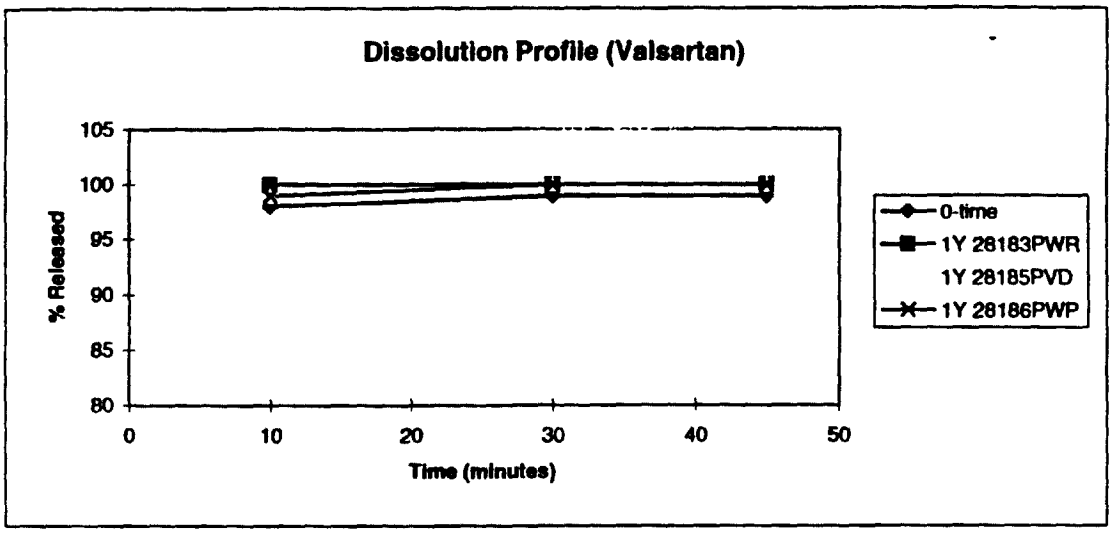


Figure 3. **Dissolution Profile on Valsartan/HCT 80/12.5mg**
Lot# L10/96 stored @ 30C/60% RH

Time (min.)	% Released (Valsartan)			
	(0-Time)	(1Y 28183)	(1Y 28185)	(1Y 28186)
10	98	100	99	99
30	99	100	100	100
45	99	100	100	100



Time (min.)	% Released (HCT)			
	(0-Time)	(1Y 28183)	(1Y 28185)	(1Y 28186)
10	91	89	91	91
30	93	91	93	95
45	94	91	93	96

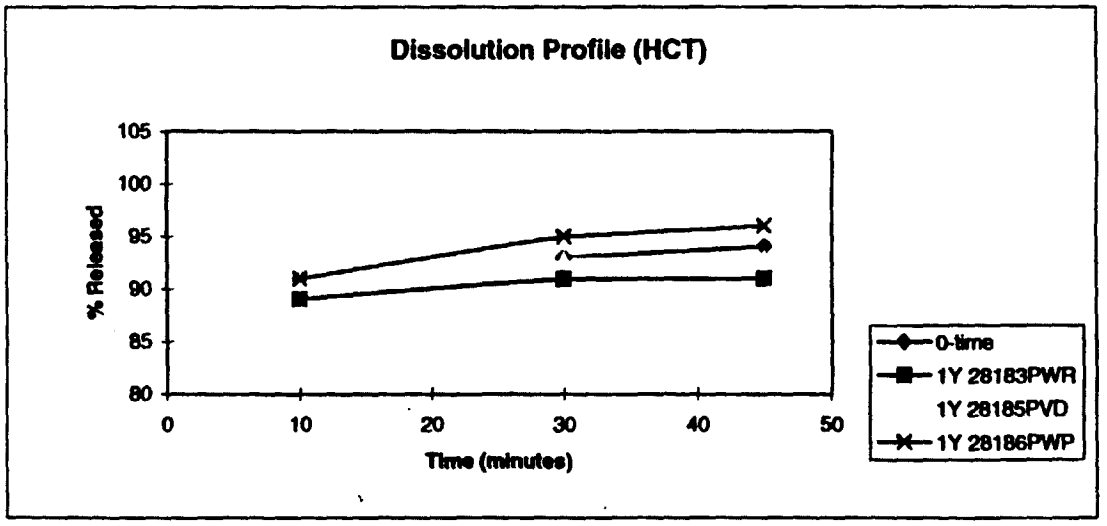
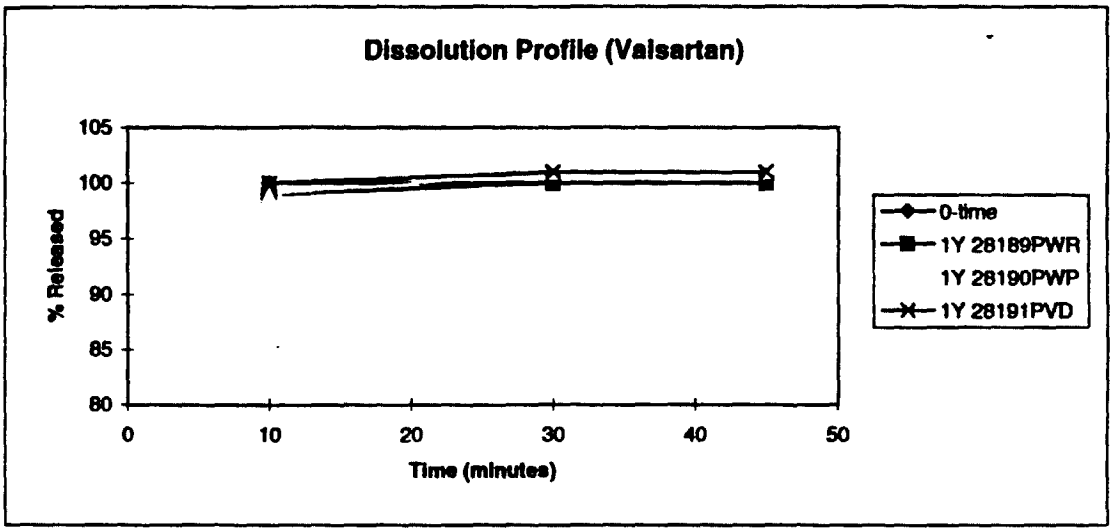


Figure 4, **Dissolution Profile on Valsartan/HCT 80/12.5mg**
Lot# L11/96 stored @ 30C/60% RH

Time (min.)	% Released (Valsartan)			
	(0-Time)	(1Y 28189)	(1Y 28190)	(1Y 28191)
10	100	99	99	100
30	100	100	101	101
45	100	100	101	101



Time (min.)	% Released (HCT)			
	(0-Time)	(1Y 28189)	(1Y 28190)	(1Y 28191)
10	91	89	90	89
30	93	90	94	91
45	94	90	95	91

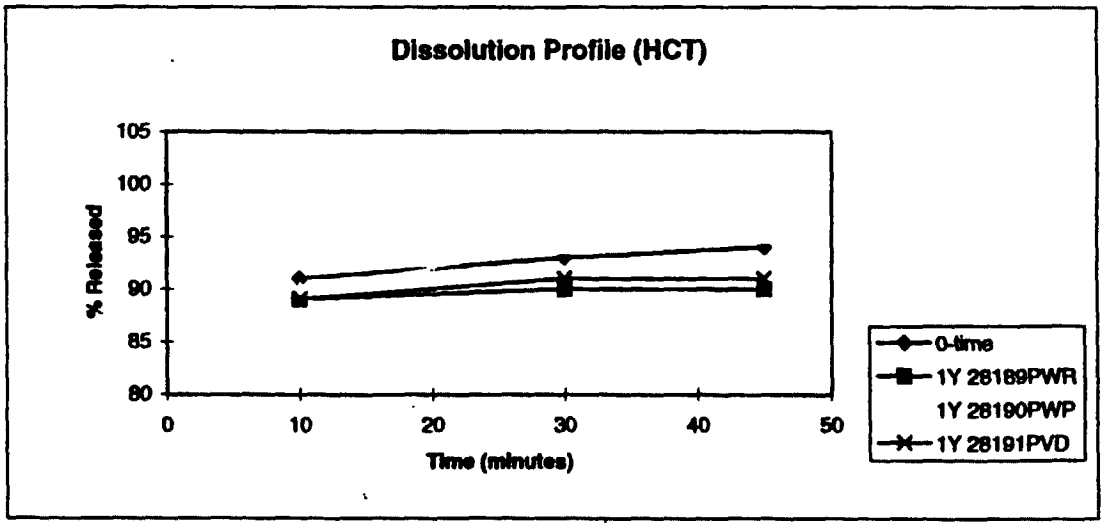
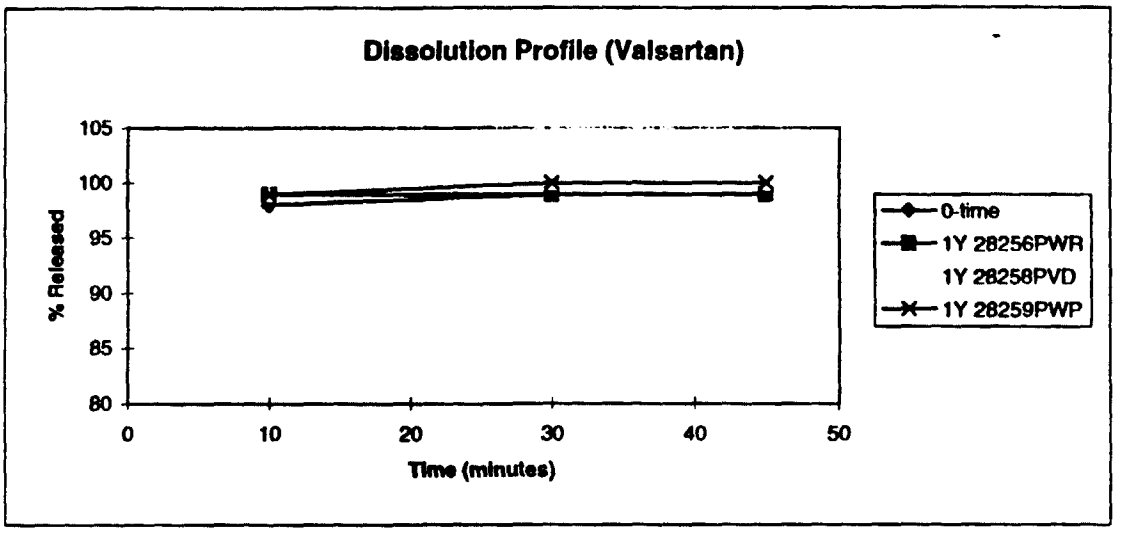


Figure 5. **Dissolution Profile on Valsartan/HCT 160/12.5mg**
Lot# L12/96 stored @ 30C/60% RH

Time (min.)	% Released (Valsartan)			
	(0-Time)	(1Y 28256)	(1Y 28258)	(1Y 28259)
10	98	99	99	99
30	99	99	100	100
45	99	99	100	100



Time (min.)	% Released (HCT)			
	(0-Time)	(1Y 28256)	(1Y 28258)	(1Y 28259)
10	91	87	88	88
30	93	89	91	93
45	93	90	92	94

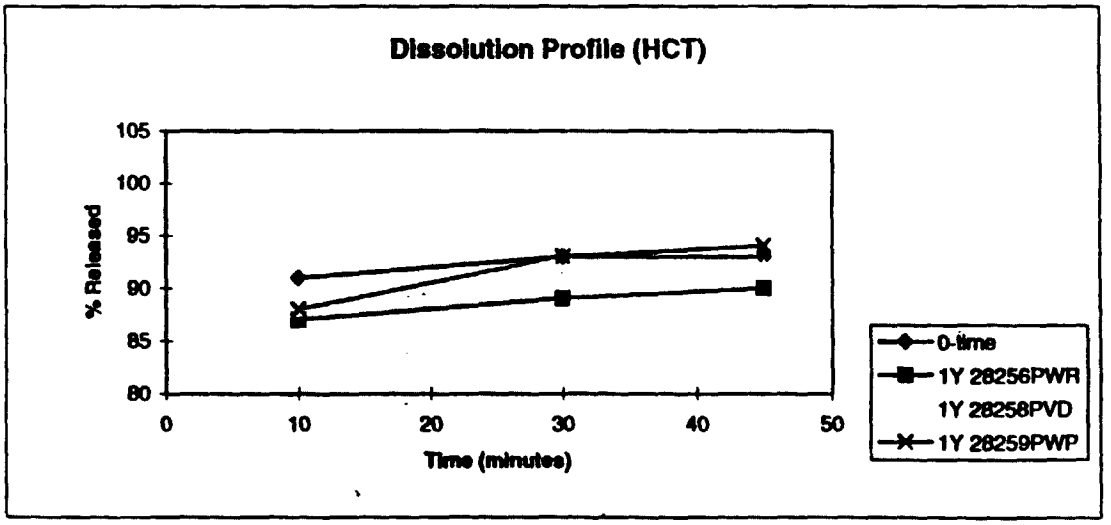
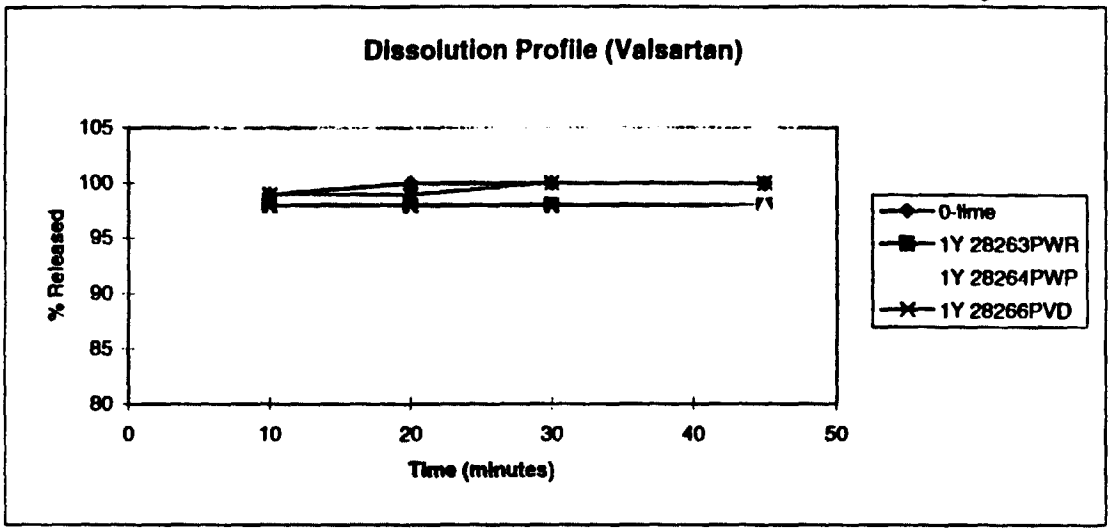
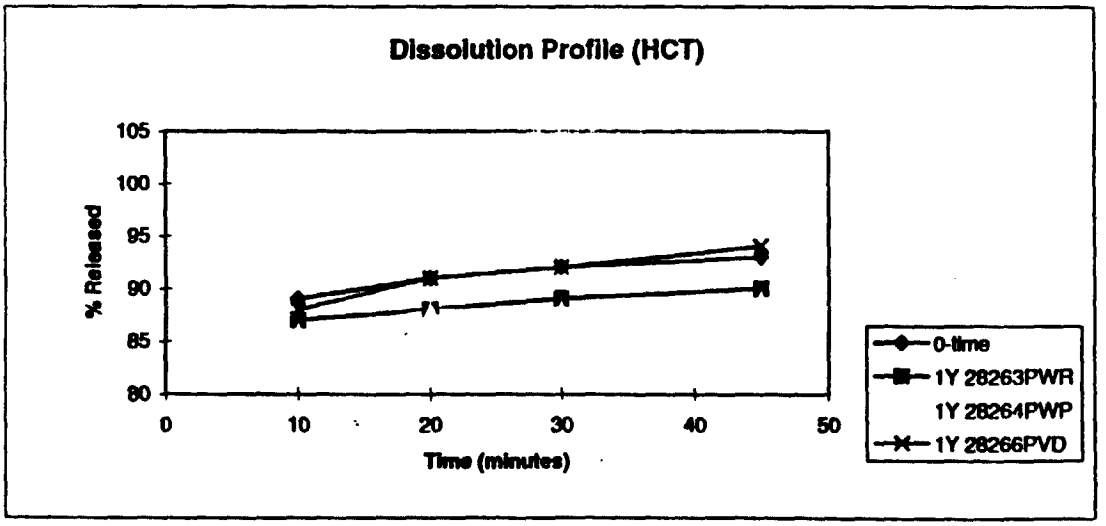


Figure 6. **Dissolution Profile on Valsartan/HCT 160/12.5mg**
Lot# L17/96 stored @ 30C/60% RH

Time (min.)	% Released (Valsartan)			
	(0-Time)	(1Y 28263)	(1Y 28264)	(1Y 28266)
10	99	98	97	99
20	100	98	97	99
30	100	98	97	100
45	100	98	98	100



Time (min.)	% Released (HCT)			
	(0-Time)	(1Y 28263)	(1Y 28264)	(1Y 28266)
10	89	87	86	88
20	91	88	88	91
30	92	89	88	92
45	93	90	89	94



K. Borgiovanni

OCT 30 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTIC REVIEW

NDA: 20-818 **SUBMISSION DATE:** MARCH 28, 1997
Diovan HTC™ (Valsartan & Hydrochlorothiazide) MAY 1, 1997
Tablets (160/12.5 and 80/12.5 mg)

NOVARTIS PHARMACEUTICALS **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: Original ~~NME~~ NDA

BACKGROUND:

Diovan™ (Valsartan) is a synthetic angiotensin II receptor antagonist recently approved (NDA 20-665) for the treatment of hypertension. The sponsor intends to market a combination tablet containing valsartan 160 mg and hydrochlorothiazide (HCTZ) 12.5 mg and valsartan 80 mg and HCTZ 12.5 mg and has submitted 2 studies that address the bioequivalence of the combination tablet compared with the separate clinical trial capsule formulations. The interaction study between valsartan and HCTZ was submitted to NDA 20-665 and showed that valsartan causes a decrease in the rate of absorption (26% decrease in Cmax and 13% decrease in Tmax) and extent of exposure (by 28%) to HCTZ. A food effect study on the combination product has not been submitted by the sponsor.

SYNOPSIS:

The sponsor has submitted two bioequivalence studies. The bioequivalence of the fixed final market image (FMI) combination tablets compared to the coadministration of the separate clinical trial capsules was assessed. Study 302 was a randomized, two-treatment, three-period, repeated-measure, crossover study with 34 subjects in which subjects received a single dose of a fixed FMI combination tablet containing 160 mg of valsartan and 12.5 mg of HCTZ and a free combination of a 160 mg capsule of valsartan and 12.5 mg capsule of HCTZ (Phase II clinical trial formulations). The FMI combination tablet was bioequivalent to the separate capsules with respect to HCTZ but bioinequivalent with respect to valsartan. The bioinequivalence with respect to valsartan is due to wider interval for AUC_{0-} (106-128) but the AUC_{0-} of the FMI tablet was only about 11% higher that than of the free combination capsule. Study 303 was a randomized, two-treatment, three-period, repeated-measure, crossover study with 35 subjects in which subjects received a single dose of a fixed FMI combination tablet containing 80 mg of valsartan and 12.5 mg of HCTZ and a free combination of a 80 mg capsule of valsartan and 12.5 mg capsule of HCTZ (Phase II clinical trial formulations). The FMI combination tablet was bioequivalent to the separate capsules with respect to both HCTZ and valsartan. The 80 mg and 160 mg valsartan capsule formulations are the clinical formulations used for NDA 20-665 and were linked to the approved valsartan formulation (although it failed with respect to Cmax of valsartan). A previous study (NDA 20-033) has established that the clinical trial HCTZ capsule formulation and commercial HCTZ (Esidrix) tablet are bioequivalent. The intra-subject variability (%CV

range) for the FMI tablets were 16.7-23.1% for AUC and 20.5-29.1% for Cmax of valsartan; 8.6-9.1% for AUC and 14.6-15.0% for Cmax of HCTZ. The intra-subject variability (%CV range) for the free combination of the clinical trial capsules were 22.1-35.1% for AUC and 28.3-39.9% for Cmax of valsartan; 9.7-15.5% for AUC and 9.9-15.2% for Cmax of HCTZ. An acceptable in vitro dissolution method has been provided but the dissolution specification should be changed from Q of at 45 minutes to Q of at 30 minutes for both valsartan and HCTZ.

STUDY SUMMARY / COMPOSITION OF FORMULATIONS AND DISSOLUTION DATA:

See Appendix

GENERAL COMMENTS TO THE MEDICAL OFFICER:

1.The sponsor has not demonstrated bioequivalence in terms of $AUC_{(0-\infty)}$ of valsartan between the combination product (valsartan 160 mg/ HCTZ 12.5 mg) and coadministration of individual valsartan 160 mg and HCTZ 12.5 mg capsules. However, PK/PD analysis (NDA 20-665) suggests that the concentration-effect relationship for valsartan is flat over a wide concentration range (400-3600 ng/ml with a dose range of 10-320 mg per day) and that pharmacokinetic differences would not have a significant effect on the efficacy of valsartan at the proposed doses (80 or 160 mg per day). In addition, the 80/12.5 mg combination tablet for which bioequivalence has been demonstrated is almost compositionally proportional to the 160/12.5 mg combination tablet. In the light of these facts the demonstration of bioequivalence in terms of $AUC_{(0-\infty)}$ of valsartan may not be very critical for deciding on the approval of the NDA.

2. Despite large food effect on valsartan (40% and 50% decrease in AUC and Cmax respectively) the Dosage and Administration section says "Diovan HCT may be administered with or without food". It is necessary to consider the fluctuation this will allow and possibly state "Diovan HCT should be administered consistently in relation to meals" to minimize fluctuation in plasma levels due to this variable. Further discussion on this with the medical officer for NDA 20-665 showed that the sponsor had conducted a clinical study that showed no food effect on efficacy of valsartan.

COMMENTS TO BE SENT TO THE FIRM:

1. The sponsor is requested to submit full dissolution profiles (sampling times at 10, 15, 30, and 45 minutes) for 1 and 2 year stability samples for both components of the formulations.

2. INTERIM DISSOLUTION SPECIFICATION: Based on the dissolution data submitted by the sponsor, the interim dissolution specifications (pending the response to request 1 above)

should be:
Q= , at 30 min for valsartan and HCTZ

3. LABELING:
a. Pharmacokinetics of HCTZ should be addressed in the label, as for valsartan.
b. Food effect study has not been conducted on the combination product. The label should state that information on the influence of coadministration with meals is not available.
c. Section on "Renal Insufficiency" for valsartan has been modified by the sponsor (see approved labeling for valsartan). Was there a basis for this? (see appendix - page 40)

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has completed the sponsor's NDA 20-818 and recommends that the dissolution specification should be changed as mentioned above. Please forward the appropriate comments the medical officer and the sponsor.

10/30/97

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. 10/30/97
CPB Briefing: 10/20/97: Malinowski, Mehta, Parekh, Huang, Williams

cc: NDA 20-818, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy), HFD-340 (Vish).

APPENDIX

THIS PAGE
WAS
DETERMINED
NO Formulations
TO BE
RELEASABLE

BIOEQUIVALENCE STUDY

STUDY NUMBER: 302 VOLUME: 1.26 PAGES: 1 - 394

INVESTIGATOR AND LOCATION:

STUDY PERIOD: AUGUST 11 - SEPTEMBER 18, 1996.

OBJECTIVE: To determine the bioequivalence in healthy subjects between a fixed final market image (FMI) combination tablet of 160 of valsartan and 12.5 mg of HCTZ (Treatment A) and a free combination of 160 mg capsule of valsartan and 12.5 mg capsule of HCTZ (Treatment B, Phase II clinical trial formulations).

FORMULATIONS:

STUDY DESIGN: Randomized, two-treatment, three-period, repeated-measure, crossover study with 30 subjects and a wash period of one week. Within each treatment sequence, the treatment from the second period was repeated in the third period (i.e., ABB or BAA). Subjects received the following treatments: single dose of a fixed FMI combination tablet containing 160 mg of valsartan and 12.5 mg of HCTZ (Treatment A), a free combination of a 160 mg capsule of valsartan and 12.5 mg capsule of HCTZ (Phase II clinical trial formulations, Treatment B. Subjects fasted overnight before and until 4 hours postdose on all of the study days. Blood samples (5 ml for valsartan and 5 ml for HCTZ) were collected at 0 (predose), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose and stored at -20°C until analysis.

ASSAYS:

Sensitivity: LOQ - 1 ng/ml.

The assays have been validated over the range of valsartan and HCTZ plasma concentrations observed in the study.

DATA ANALYSIS: AUC_{0-48}, $AUC_{0-\infty}$, C_{max}, $t_{1/2}$, and T_{max}, were calculated.

RESULTS: Tables 1 and 2 summarize the pharmacokinetic data obtained from the study while Figures 1 and 2 show the mean plasma concentration-time profiles following the two treatments.

Table 1. Mean (SD) Parameter Values for Valsartan Following Oral Administration of FMI Tablet and Clinical Capsules to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	90% CI
Cmax (ng/ml)	3603 (1828)	3287 (1799)	99 - 124
$AUC_{(0-48)}$ (ng*h/ml)	22410 (11409)	20473 (10044)	104 - 124
$AUC_{(0-\infty)}$ (ng*h/ml)	24028 (11313)	21568 (10296)	106 - 128
$T_{1/2}$ (h)	11.9 (8.0)	11.2 (5.0)	-
T_{max} (h)*	3.0	3.0	-

TREATMENT A = One FMI Tablet
TREATMENT B = Clinical Capsules
*Median value

Figure 1: Mean ± SD plasma valsartan concentration-time profiles following a single dose of 160 mg of valsartan and 12.5 mg of HCTZ in healthy subjects .

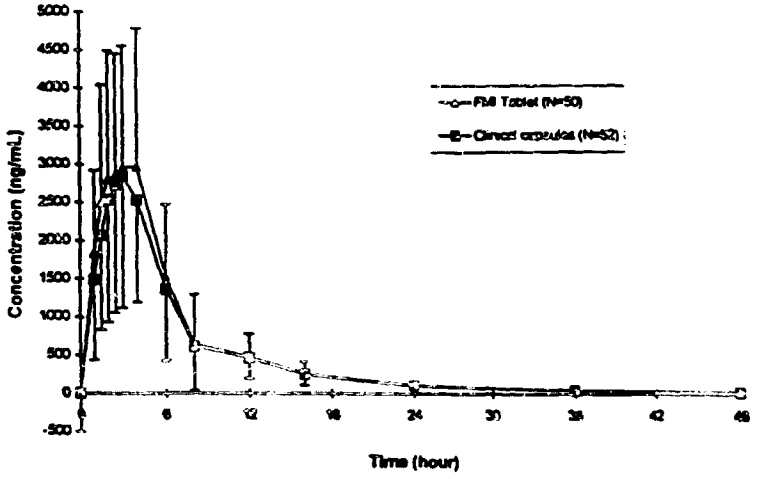
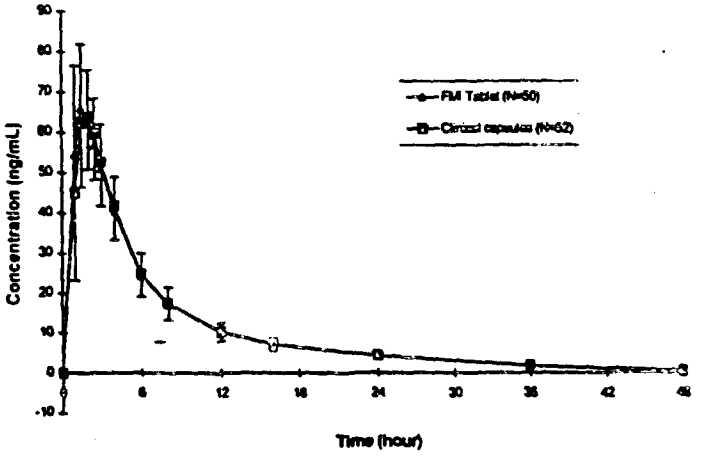


Table 2 . Mean (SD) Parameter Values for HCTZ Following Oral Administration of FMI Tablet and Clinical Capsules to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	90% CI
Cmax (ng/ml)	69.2 (20)	69.0 (14)	96 - 107
$AUC_{(0-48)}$ (ng*h/ml)	481.6 (93)	483.1 (87)	96 - 104
$AUC_{(0-\infty)}$ (ng*h/ml)	487.4 (97)	491.4 (918)	96 - 104
$T_{1/2}$ (h)	10.2 (2.0)	10.5 (2.0)	-
T_{max} (h)*	1.5	1.8	-

TREATMENT A = One FMI Tablet
TREATMENT B = Clinical Capsules
*Median value

Figure 2: Mean ± SD plasma HCTZ concentration-time profiles following a single dose of 160 mg of valsartan and 12.5 mg of HCTZ in healthy subjects .



CONCLUSIONS: The FMI fixed combination tablet conataining 160 mg valsartan and 12.5 mg HCTZ is bioinequivalent to free combination of one 160 mg valsartan clinical capsule and one 12.5 mg HCTZ with respect to valsartan but bioequivalent with respect HCTZ. The bioinequivalence with respect to valsartan is due to wider interval for $AUC_{0-\infty}$ (106-128) but the $AUC_{0-\infty}$ of the FMI tablet was only about 11% higher that than of the free combination capsule. However, PK/PD analysis (NDA 20-665) suggests that the concentration-effect relationship for valsartan is flat over a wide concentration range (400-3600 ng/ml with a dose range of 10-320 mg per day) and that pharmacokinetic differences would not have a significant effect on the efficacy of valsartan at the proposed doses (80 or 160 mg per day). In addition, the 80/12.5 mg combination tablet for which bioequivalence has been demonstrated is almost compositionally proportional to the 160/12.5 mg combination tablet. In the light of these facts the demonstration of bioequivalence in terms of $AUC_{(0-\infty)}$ of valsartan may not be very critical for deciding on the approval of the NDA.

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BIOEQUIVALENCE STUDY

STUDY NUMBER: 303 VOLUME: 1.27 PAGES: 1 - 412

INVESTIGATOR AND LOCATION:

STUDY PERIOD: JULY 1 - AUGUST 7, 1996.

OBJECTIVE: To determine the bioequivalence in healthy subjects between a fixed final market image (FMI) combination tablet of 80 of valsartan and 12.5 mg of HCTZ (Treatment A) and a free combination of 80 mg capsule of valsartan and 12.5 mg capsule of HCTZ (Treatment B, Phase II clinical trial formulations).

FORMULATIONS:

STUDY DESIGN: Randomized, two-treatment, three-period, repeated-measure, crossover study with 35 subjects and a wash period of one week. Within each treatment sequence, the treatment from the second period was repeated in the third period (i.e., ABB or BAA). Subjects received the following treatments: single dose of a fixed FMI combination tablet containing 80 mg of valsartan and 12.5 mg of HCTZ (Treatment A), a free combination of a 80 mg capsule of valsartan and 12.5 mg capsule of HCTZ (Phase II clinical trial formulations, Treatment B. Subjects fasted overnight before and until 4 hours postdose on all of the study days. Blood samples (5 ml for valsartan and 5 ml for HCTZ) were collected at 0 (predose), 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose and stored at -20°C until analysis.

ASSAYS:

observed in the study.

DATA ANALYSIS: AUC_{0-48}, $AUC_{0-\infty}$, C_{max}, $t_{1/2}$, and T_{max}, were calculated.

RESULTS: Tables 1 and 2 summarize the pharmacokinetic data obtained from the study while Figures 1 and 2 show the mean plasma concentration-time profiles following the two treatments.

Table 1. Mean (SD) Parameter Values for Valsartan Following Oral Administration of FMI Tablet and Clinical Capsules to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	90% CI
Cmax (ng/ml)	1641 (841)	1447 (814)	87 - 112
$AUC_{(0-48)}$ (ng*h/ml)	10560 (5157)	9293 (4787)	91 - 112
$AUC_{(0-\infty)}$ (ng*h/ml)	10374 (5091)	9574 (4925)	88 - 110
$T_{1/2}$ (h)	5.2 (2.0)	6.2 (4.0)	-
T_{max} (h)*	3.0	2.5	-

TREATMENT A = One FMI Tablet
TREATMENT B = Clinical Capsules
*Median value

Figure 1: Mean ± SD plasma valsartan concentration-time profiles following a single dose of 80 mg of valsartan and 12.5 mg of HCTZ in healthy subjects .

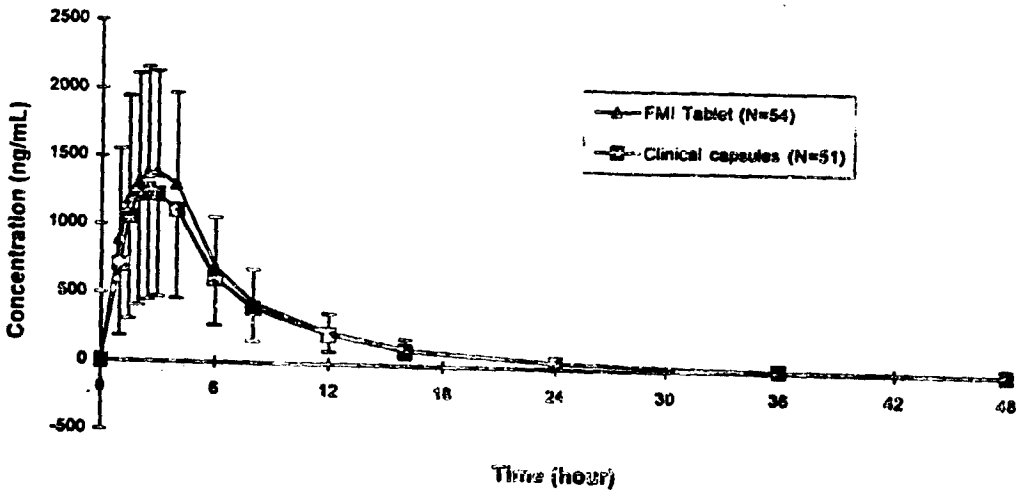
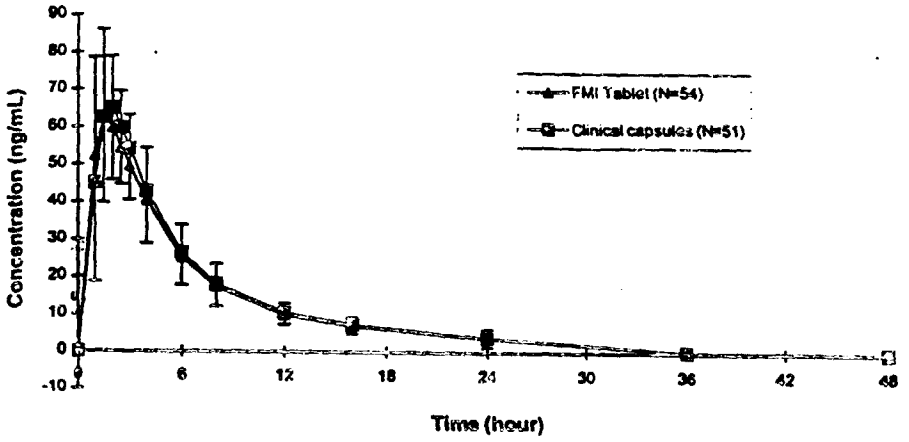


Table 2 . Mean (SD) Parameter Values for HCTZ Following Oral Administration of FMI Tablet and Clinical Capsules to Healthy Volunteers

PARAMETER	TREATMENT A	TREATMENT B	90% CI
Cmax (ng/ml)	68.7 (21)	72.1 (20)	86 - 96
$AUC_{(0-48)}$ (ng*h/ml)	450.51 (118)	466.5 (140)	92 - 100
$AUC_{(0-\infty)}$ (ng*h/ml)	450.54 (118)	466.5 (140)	92 - 100
$T_{1/2}$ (h)	8.6 (2.0)	8.85 (3.0)	-
T_{max} (h)*	1.5	2.0	-

TREATMENT A = One FMI Tablet
TREATMENT B = Clinical Capsules
*Median value

Figure 2: Mean ± SD plasma HCTZ concentration-time profiles following a single dose of 80 mg of valsartan and 12.5 mg of HCTZ in healthy subjects .



CONCLUSIONS: The FMI fixed combination tablet conataining 80 mg valsartan and 12.5 mg HCTZ is bioequivalent to free combination of one 80 mg valsartan clinical capsule and one 12.5 mg HCTZ with respect to valsartan and HCTZ.