CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-314

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-314
DATE RECEIVED BY CENTER:	6/30/2008
DRUG PRODUCT:	EXFORGE® HCT Tablets
DRUG SUBSTANCE:	Amlodipine Besylate, Valsartan and Hydrochlorothiazide
INTENDED CLINICAL POPULATION:	Hypertensive
SPONSOR:	Novartis Pharmaceuticals Corporation
REVIEW DIVISION:	Division of Cardiovascular and Renal Products
PHARM/TOX REVIEWER:	G. Jagadeesh, Ph.D.
PHARM/TOX SUPERVISOR:	Charles Resnick, Ph.D.
DIVISION DIRECTOR:	Norman Stockbridge, M.D., Ph.D.
PROJECT MANAGER:	Nguyen Quynh
Date of review submission to DFS:	November 5, 2008

NDA number: 22,314
Date of Submission: EDR, 6-28-2008
Center Receipt Date: 6-30-2008
Reviewer Receipt Date: 8-11-2008
Sponsor: Novartis Pharmaceuticals Corporation
Manufacturer of Drug Substance: [redacted] b(4)

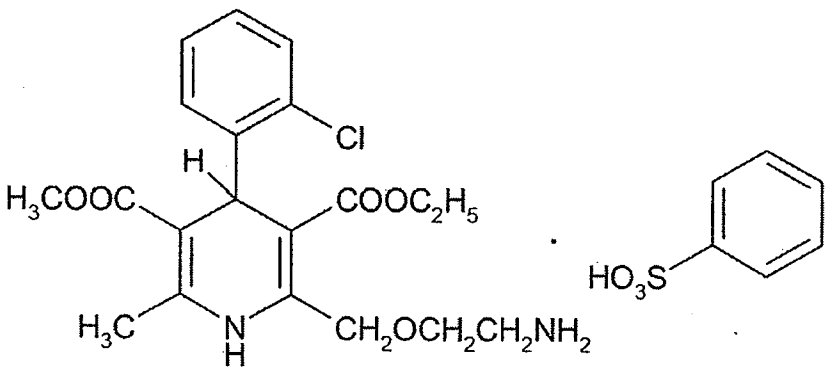
Manufacturer of Drug Product: Novartis Pharmaceuticals Corporation

Reviewer: G. Jagadeesh, Ph.D.
Division: Division of Cardiovascular and Renal products
Review completion date: October 28, 2008

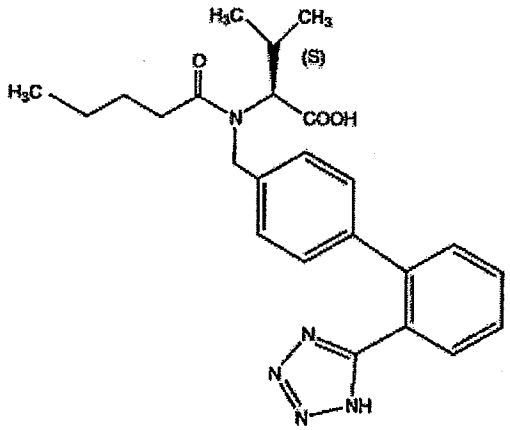
Drug Product: VEA489, EXFORGE® HCT Tablets

Drug Substances

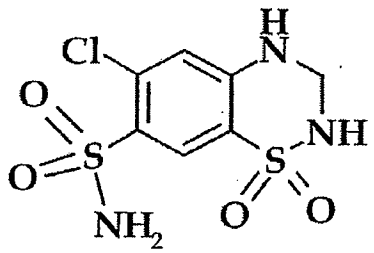
Generic name: **Amlodipine Besylate**
Chemical name: (*RS*)-2-[(2'-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl ester, 5-methyl ester, benzene sulfonate.
Chemistry: Amlodipine is a racemic mixture (R and S isomers). It is a white to pale yellow crystalline powder slightly soluble in water and sparingly soluble in ethanol.
CAS registry number: 1114790-99-6 (besylate salt form)
88150-42-9 (free base form)
Molecular formula/molecular weight: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_5SO_3H$ / 567.06 (besylate)



Generic name: **Valsartan**
Code name: CGP 48933
Chemical name: (*S*)- N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine.
Chemistry: Valsartan contains two acidic functions and includes one asymmetric center. It is free diacid, hydrophilic and the pure *S*-enantiomer. The corresponding (R)-enantiomer is less active in biological tests. It is a white, microcrystalline and soluble in water.
CAS registry number: 173334-58-2
Molecular formula/molecular weight: $C_{24}H_{29}N_5O_3$/ 435.5 (free base)



Generic name: **Hydrochlorothiazide (HCTZ)**
Chemical name: 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
Chemistry: Hydrochlorothiazide is a white, or practically white, crystalline powder which is slightly soluble in water and freely soluble in sodium hydroxide solution.
CAS registry number: 58-93-5
Molecular formula/molecular weight: $C_7H_8ClN_3O_4S_2$ / 297.74



Related Applications: Clinical trials supporting the current NDA were conducted under Novartis' IND 65,174. Novartis' NDA 20,665 for Valsartan (Diovan®) was approved for the treatment of hypertension in 1996. Pfizer's NDA 19,787 for racemic amlodipine besylate (Norvasc®) was approved for the treatment of hypertension, chronic stable angina and vasospastic angina in 1992. Novartis' NDA 20,818 for Valsartan/HCTZ (Diovan® HCT) and Novartis' NDA 21,990 for Valsartan/ amlodipine (Exforge®) were approved for the treatment of hypertension in 1998 and June 2007, respectively.

Drug Class: Valsartan: Angiotensin II receptor class 1 (AT_1 receptor) antagonist
Amlodipine: Dihydropyridine calcium channel blocker
Hydrochlorothiazide: Thiazide diuretic

Intended Clinical Population: Hypertensive subjects

Clinical Formulation: The film-coated tablets are formulated in five strengths with amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free-base combined with 160 or 320 mg of valsartan, and 12.5 or 25 mg of HCTZ. The following table lists proposed final commercial formulations.

COMPOSITION OF AMLODIPINE BESYLATE, VALSARTAN AND HCTZ FILM-COATED TABLET

Ingredient	5/160/12.5 mg 6001954	10/160/12.5 mg 6002195	5/160/25 mg 6002194	10/160/25 mg 6001955	10/320/25 mg 6002196
Component (mg)					
Amlodipine besylate					
Valsartan					
Hydrochlorothiazide					
Microcrystalline cellulose					
Crospovidone					
Magnesium stearate					
Tablet core weight					
Basic coating premix - white					
Basic coating premix - yellow					
Basic coating premix - red					
Water, purified[2]					
Coating weight					
Total tablet weight					

b(4)

Crospovidone: ((colloidal anhydrous: , Magnesium stearate: . hypromellose, iron oxides, polyethylene glycol, talc and titanium dioxide.

Route of Administration: Oral

Proposed Dosage Regimen: One tablet daily.

Disclaimer: Unless indicated otherwise, tables and graphs (with or without editorial corrections by the reviewer) are taken from the sponsor's submission.

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EXECUTIVE SUMMARY

I. Background

The rationale for combining two or more antihypertensive agents from different pharmacologic classes is based on the expectation that the combination will exert an additive or synergistic antihypertensive effect when compared to single drug treatment. Such combinations permit simultaneous targeting of multiple physiological systems involved in the regulation of blood pressure. In addition, combining two or more agents may improve patient compliance and enhance tolerability by reducing the incidence of certain side effects that are more prevalent when the drugs are used alone. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has emphasized the importance of achieving blood pressure goals through aggressive treatment with multiple medications, if needed.

Novartis has developed a triple fixed combination (VEA489, Exforge® HCT) of valsartan (AT-1 receptor antagonist), hydrochlorothiazide (diuretic), and amlodipine besylate (calcium channel blocker) for the treatment of hypertension for patients not adequately controlled on any kind of dual combination. All three components are currently marketed for the treatment of hypertension.

II. Recommendations

A. **Recommendation on Approvability:** Approvable

B. **Recommendations for Additional Nonclinical Studies:** None

C. **Recommendations for Labeling:** The sections of the proposed labeling (EDR version dated June 30, 2008) that deal with nonclinical studies are considered satisfactory.

III. Summary of Nonclinical Findings

The sponsor has not performed pharmacology or ADME studies for the combination product. To support the chronic administration of the valsartan/amlodipine besylate/HCTZ combination to adult hypertensive patients, a 13 week repeat dose toxicity study was performed in Wistar-Hannover rats. In this study, valsartan, amlodipine and HCTZ were administered orally, by gavage, separately and together at a ratio of 16:1:2.5. (All doses and dose ratios in this review are presented in terms of the amlodipine base.)

Daily administration of valsartan, amlodipine besylate and HCTZ at doses of 8:0.5:1.25 or more mg/kg/day for 13 weeks resulted in 6 deaths or sacrifices in moribund condition (includes 1 each in the group receiving valsartan or HCTZ alone). All deaths were accidental and unrelated to treatment. The target organs of toxicity in both sexes were stomach (minimal erosions) and kidneys (hyperplasia of the juxtaglomerular apparatus). In addition, a significant increase in BUN (<2-fold) and a decrease in erythroid parameters relative to

control were noted for both sexes receiving the combination drugs or valsartan alone. These effects were not noted in recovery group animals. All of these effects are attributed to known effects of valsartan. Additional findings included dose-dependent and statistically significant decreases in mean body weight gain and food consumption relative to control for both sexes and all dose combinations, for the duration of the study. Most of the target organ toxicities, according to the sponsor, were associated with excessive pharmacological effects of valsartan, amlodipine, and/or HCTZ. However, there is no data in the submission to support this argument. The incidence and severity of adverse effects were slightly greater for the combination than for valsartan, amlodipine besylate or HCTZ alone.

The pharmacokinetics of valsartan, HCTZ and amlodipine in rats (likewise in humans) are similar when administered alone or when administered as the double or triple combinations. Systemic exposures (AUCs) to valsartan:amlodipine:HCTZ in rats treated with the combination were compared to systemic exposures in humans treated at the highest combination doses of valsartan (320 mg), amlodipine (10 mg) and HCTZ (25 mg). Exposures to 8 mg valsartan/0.5 mg amlodipine/1.25 mg HCTZ/kg/day in rats (highest dose not resulting in glandular stomach erosion or JGA hyperplasia) were far lower than exposure in humans (0.06 to 0.13 times, based on AUC values), indicating the absence of a safety margin for humans. However, the combination product can still be used safely in humans for the treatment of hypertension because the target organ toxicities are monitorable and attributable to the individual drugs of the combination, drugs which are currently approved for use in this patient population and have often been used concomitantly.

PHARMACOLOGY/TOXICOLOGY REVIEW

1.0. PHARMACODYNAMICS: NO STUDIES CONDUCTED

2.0. DRUG DISPOSITION: NO STUDIES CONDUCTED

3.0. TOXICOLOGY

3.1. Repeat Dose Toxicity

3.1.1. 13 Week Oral Gavage Study in Rats With a 4 Week Recovery

Key Study Findings: There were 6 deaths, none of which were attributed to drug treatment. Dose-dependent decreases in mean body weight gain relative to concurrent control were noted for both sexes with all dose combinations for the entire duration of the study. A decrease in erythroid parameters relative to control was noted for both sexes dosed with the mid or high dose combination or valsartan alone. Hyperplasia of the juxtaglomerular apparatus along with a moderate (<2-fold) increase in BUN was noted in both sexes at VEA489 doses of 32:5:2 or more mg valsartan:HCTZ:amlodipine/kg/day and with valsartan alone. Focal erosions of the glandular stomach were noted in males treated with valsartan alone or in combination with HCTZ and amlodipine at 32:5:2 or more mg/kg/day. None of these effects were noted in recovery group animals. The VEA489 NOAEL was considered to be 8:1.25:0.5 mg/kg/day.

Study No.: 0670715
Location of Report: EDR
Conducting Laboratory and Location: Safety Profiling and Assessment Facilities, Novartis Pharmaceuticals Corporation, East Hanover, NJ.
Dates of Study: The animals were initially dosed on June 19, 2007 and necropsied September 22 (main study groups) or October 22, 2007 (recovery groups).
GLP Compliance: Yes
QA'd Report: yes (X) no ( )
Drug, Lot #: Valsartan, batch #C0657, 99.5% pure; Hydrochlorothiazide, batch #C0095, 100% pure; Amlodipine besylate, batch #000884205H, 100% pure.
Formulation: The drugs were suspended in 0.5% (w/v) hydroxypropylcellulose —— aqueous solution and the suspensions prepared weekly. Analysis of the formulations for achieved concentration and homogeneity was performed for each drug in weeks 1 and 13, and for HCTZ also in weeks 3 and 4. b(4)

Animals

Species/Strain: Rats, IGS Wistar Hannover (Crl:WI(Han), from —— b(4)
Number: 10/sex/group. An additional 6 animals/sex/group were included for the control and high dose combination groups to serve as recovery animals for the 4 week recovery period.
Age: 8 weeks old at initiation of dosing

Weight: Males: 232.6-279.4 gm, Females: 159.1-196.4 gm, at initiation of dosing
Husbandry: Animals were housed in same sex pairs, except during the urine collection period and on the day prior to scheduled necropsy. Food and water were available *ad libitum* except for study defined fasting procedures and during the urine collection period.

Dosing

Doses: Valsartan, HCTZ and amlodipine (VEA489) were administered (at a ratio of 16:2.5:1) at doses of 8:1.25:0.5, 32:5:2 or 64:10:4 mg/kg/day. Three additional groups of rats received valsartan, HCTZ or amlodipine at 64, 10 or 4 mg/kg/day, respectively. Control group received the vehicle (Table 3.1.1.1). The doses were selected on the basis of a 2 week oral study in Wistar rats in which gavage administration of VEA489 at doses of 256:40:16 more mg/kg/day resulted in deaths of 2 of 5 females on study days 5 and 10. All males and the surviving females were sacrificed on day 10. Erosions of the glandular stomach were noted for both sexes in this dose group. Significant decreases in mean body weight gain in both sexes that ranged from 48 to 88%, relative to control were noted at doses of 64:10:4 or more mg/kg/day. There were also decreases in erythroid parameters and increases in serum urea nitrogen and creatinine at doses of 128:20:8 or more mg/kg/day. Microscopically, glandular stomach erosions and thymic lymphoid depletion at 256:40:16 mg/kg/day and decreased hematopoiesis in the spleen at 128:20:8 or more mg/kg/day was noted.

TABLE 3.1.1.1
STUDY DESIGN

Group	Number/sex	Animal numbers		Dose* (mg/kg/day) V:E:A	Concentration (mg/mL) V:E:A
		males	females	Base/(Salt)**	Base/(Salt)**
1	10	1001-10	1501-10	0	0
Control	+6 recovery	1011-16	1511-16		
2	10	2001-10	2501-10	8:1.25:0.5 (0.7)	1.6:0.25:0.1 (0.14)
Low Comb.					
3	10	3001-10	3501-10	32:5:2 (2.8)	6.4: 1 : 0.4 (0.6)
Mid Comb.					
4	10	4001-10	4501-10	64:10:4 (5.5)	12.8 :2: 0.8 (1.1)
High Comb.	+6 recovery	4011-16	4511-16		
5	10	5001-10	5501-10	64	12.8
High Valsartan					
6***	10	6001-10	6501-10	10	2
High HCT					
7	10	7001-10	7501-10	4 (5.5)	0.8 (1.1)
High Amlodipine					

*V:E:A = valsartan:esidrex:amlodipine; Doses were not corrected for active moiety.
**Salt/base ratio for amlodipine besylate = 1.387.
*** Based on the analytical chemistry laboratory results during weeks 1 and 3, the doses received during this time frame may have been less than 10 mg/kg/day. This occurrence is recognized as a protocol deviation.

Route, Mode and Duration of Administration: Orally by gavage (5 ml/kg), once daily, for 13 weeks. Recovery phase animals were treated for the same duration but were killed 4 weeks later.

Observations and Measurements

Clinical Signs: All animals were observed twice daily (prior to dosing and at approximately 1.5 to 3 hr postdose) for clinical signs and mortality.
Body Weight and Food Consumption: Recorded once before treatment and once weekly during the dosing and recovery periods.
Ophthalmology: Conducted once pretest and on all surviving control and high dose animals (groups 1, 4 to 7) during week 13.
Hematology and Clinical Biochemistry: Blood samples were collected from all surviving animals in weeks 5/6, 13 and recovery week 4 for hematology (erythrocytes, hematocrit, hemoglobin, Wintrobe indices, red cell distribution width, reticulocytes, white blood cell count, white blood cell differential, platelets) and blood chemistry (ALT, AST, AP, total bilirubin, total protein, albumin, globulins, glucose, BUN, creatinine, creatine kinase, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol, A/G ratio) examinations. Blood was drawn from the sublingual vein under light isoflurane anesthesia.
Urinalysis: Urine samples were collected from individual animals for up to 5 hr and analyzed for specific gravity, bilirubin, blood, glucose, ketones, protein, urobilinogen, pH). Food and water were removed during collection.
Pathology: Animals were fasted overnight prior to terminal necropsy and weighed before sacrifice. A complete necropsy was conducted on all animals with a recording of macroscopic observations for all tissues listed in Table 3.1.1.2. At scheduled sacrifices, blood samples were collected under anesthesia for genomics from all surviving animals from vena cava and abdominal aorta. Organ weights were recorded only at scheduled sacrifices. Immediately after weighing, samples from the liver, kidney, spleen and stomach were frozen for possible investigational gene expression analysis[1]. Microscopic examinations were performed on all tissues listed in Table 3.1.1.2 from all animals in the control and high dose non-recovery groups (groups 1, 4 to 7) and for all unscheduled deaths/sacrifices. Additionally, all macroscopic lesions and target organs (kidneys, spleen, stomach and thymus) were processed for microscopic evaluation from all animals including recovery groups.
Toxicokinetics: Blood samples were collected from the sublingual vein of the non-recovery animals under light isoflurane anesthesia on day 1/2 and in week 11 at 0.5, 1, 2, 6 and 24 hr after dosing (2 rats/sex/group/time point).

[1] Gene expression analyses were not considered a part of this study and thus were not included in this report.

TABLE 3.1.1.2

Tissue list for collection, weighing (W), processing (P) and/or genomics (G)

W		P	adrenal	W		P	ovary (with oviduct*)
		P	aorta			P	pancreas
		P	bone marrow (in bone)			P	parathyroid
		P	bone marrow smear	W		P	pituitary
W		P	brain	W		P	prostate
		P	cecum			P	rectum
		P	cervix			P	salivary gland
		P	colon			P	sciatic nerve
		P	duodenum			P	seminal vesicle
		P	epididymis			P	skeletal muscle
		P	esophagus			P	skin
		P	eye			P	spinal cord
		P	femur/tibia	W	G	P	spleen
		P	harderian gland			P	sternum
W		P	heart		G	P	stomach
		P	ileum	W		P	testis
		P	jejunum	W		P	thymus
W	G	P	kidney	W		P	thyroid
		P	lacrimal gland			P	tongue
		P	larynx-cross section			P	trachea
W	G	P	liver			P	ureter-cross section*
		P	lung			P	urinary bladder
		P	lymph node - bronchial	W		P	uterus
		P	lymph node - mandibular			P	vagina
		P	lymph node - mesenteric			P	macroscopic lesions
		P	mammary gland area				animal identification
			nasal passage		G		blood

* bilateral collection, unilateral histopathology

Results

Analysis of Formulations: All individual drug preparations were stable for 4 hr stirring at room temperature, 1 day stored at room temperature, and 12 days stored at 6°C. The uniformity and concentration of the HCTZ formulation prepared in weeks 1 and 3 were outside of specifications (83 ± 12.2% and 78% ± 2.9% of target, respectively). The specification for concentration was ± 15% of target concentration. Though this is considered a protocol deviation, the sponsor asserts that it does not impact the study since the objective of the study was to assess the toxicity of VEA489 in combination and all formulation results in the triple combination preparations were within acceptable limits.
Mortality: Seven animals (including 1 control) died during the study. All deaths were attributed to anesthesia overdose during bleeding procedures or accidental injury due to gavage errors (Tables 3.1.1.3 and 3.1.1.4).

TABLE 3.1.1.3
SUMMARY OF MORTALITY IN MALES

Group (Sex)	1 (M)	2 (M)	3 (M)	4 (M)	5 (M)	6 (M)	7 (M)
Dose*	0	8:1.25:0.5	32:5:2	64:10:4	64	10	4
Found dead (animal no.)	1** (1001)	0	1*** (3005)	0	0	0	0

*Dose (mg/kg/day) = valsartan:esidrex:amlodipine

**Secondary to dosing trauma

***Found dead/cannabilized.

TABLE 3.1.1.4
SUMMARY OF MORTALITY IN FEMALES

Group (Sex)	1 (F)	2 (F)	3 (F)	4 (F)	5 (F)	6 (F)	7 (F)
Dose*	0	8:1.25:0.5	32:5:2	64:10:4	64	10	4
Found dead/due to bleed (animal nos.)	0	1 (2503)	0	2 (4505, 4506)	1 (5505)	0	0
Found dead/cannabilized (animal no.)	0		0			1** (6504)	0

*Dose (mg/kg/day) = valsartan:esidrex:amlodipine

**Secondary to dosing trauma

Clinical Signs: No test substance-related clinical signs were noted during the treatment or recovery periods. A male in the mid dose combination group (#3005) displayed clinical signs of dehydration and mucoid feces on study day 35 and died on day 36. The sponsor attributed this condition to a urinary tract obstruction not related to test substance administration.

Body Weights: A dose-dependent decrease in mean body weight gain relative to concurrent control was noted for males and females at all dose combinations. Mean body weight at the end of the dose period (day 92) for mid and high dose combination groups was statistically significantly different from the control group for both sexes. Body weights of treated groups had caught up with control weights by recovery day 29.

TABLE 3.1.1.3
MEAN BODY WEIGHT AND BODY WEIGHT GAIN RELATIVE TO CONTROL

Dose combination	Sex	Body weight		Body weight gain	
		(-) % change	Study day	(-) % change	Study day
Low dose	M	5-8	22-92*, 64	17-22	15-36, 57, 64, 92
	F	2.4*	22-92*	9	92*
Mid dose	M	5-10	15, 36-92	19-24	8-92
	F	7-9	29, 57, 71, 85, 92	24-40	15-36, 50-92
High dose	M	6-10	8-92	21-46	8-92
	F	7-9	22-36, 50-92	24-55	8-92

All per cent changes are significant unless noted by an asterisk ($p > 0.05$).

Food Consumption: Statistically significant decreases in mean food consumption relative to control were noted for males (8 to 10%) and females (7 to 16%) in the mid and high dose combination groups on most dosing days. The decreases in food consumption correlated with the decreases in mean body weight gain. Mean food consumption during the recovery period for both sexes was comparable to consumption of control animals.

There were no effects on food consumption when each test substance was administered alone.

Ophthalmoscopy: No remarkable ocular changes

Hematology: Statistically significant nondose-dependent decreases in erythroid parameters relative to control were noted for females in mid and high dose combination and valsartan alone groups. The erythroid parameters of recovery group animals were comparable to the concurrent control.

Clinical Chemistry: A significant increase in mean levels of blood urea nitrogen (up to 1.8-fold) was noted in both sexes receiving the combination at 32:5:2 or more mg/kg/day, HCTZ alone, and males receiving valsartan alone at 64 mg/kg/day (Table 3.1.1.4). Values were comparable to concurrent control values at the end of the recovery period.

TABLE 3.1.1.4
EFFECT OF VEA489 ON BLOOD UREA NITROGEN

Parameter	Dose (mg/kg/day)									
	Control		32:5:2		64:10:4		Valsartan		HCTZ	
	M	F	M	F	M	F	M	F	M	F
Urea (mg/dL) d31	16.8	19.1	19.6*	29.4§	26.6§	33.8§	21.0§	20.2	16.6	19.4
Urea (mg/dL) d86	13.6	15.1	16.7	21.4§	23.8§	24.2§	15.0	15.8	16.4§	17.9§

Urinalysis: No significant changes.

Organ Weights: Statistically significant and nondose-dependent decreases (17 to 20% below vehicle control) in mean absolute and relative (to body and/or brain) heart weights with no histopathological correlate were noted in males at all combination doses and in females at 32:5:2 or more mg/kg/day and in both sexes given valsartan alone. This weight difference was no longer present at the end of the recovery period.

Gross Pathology: There were no treatment-related macroscopic changes.

Histopathology: Main histopathological findings considered directly related to treatment were noted in the kidneys and stomach. In kidneys, dose-dependent increased incidence and severity (relative to control) of hyperplasia of the juxtaglomerular apparatus (JGA) was noted in both sexes receiving valsartan alone or in combination with HCTZ and amlodipine at doses of 32:5:2 or more mg/kg/day. Focal tubular basophilia and mineralization were noted with low incidence in both control and drug treated groups. Focal erosions of the glandular stomach were noted in males treated with valsartan alone or in combination with HCTZ and amlodipine at 32:5:2 or more mg/kg/day. Except for basophilic tubules none of the changes were present in the recovery group (Table 3.1.1.5). Both renal and stomach lesions were attributed by the sponsor to the excessive pharmacological action of valsartan at the doses employed in this study.

TABLE 3.1.1.5
SELECTED TREATMENT-RELATED MICROSCOPIC FINDINGS FOR BOTH SCHEDULED AND UNSCHEDULED SACRIFICES

Parameter	Dose (valsartan:HCTZ:amlodipine mg/kg/day)							
	Control		32:5:2		64:10:4		V	
	M	F	M	F	M	F	M	F
No of animals evaluated at 13 wk	10	10	10	10	10	10	11	11
(No of animals evaluated 4 wk postdose)	(6)	(6)			(6)	(6)	(5)	(5)
Kidney								
Hyperplasia, JGA	0	0	3	4	9	8	2	5
Basophilic, tubule	2	0	1	0	3	0	0	0
	(1)	(0)			(3)	(2)		
Mineralization	0	2	1	1	0	4	0	4
	(0)	(0)			(0)	(1)		
Stomach								
Erosion, glandular	0	0	1	0	2	0	1	0
Vacuolation, cytoplasmic	3	2	3	1	4	2	5	2

Toxicokinetics: The number of animals per time point was small enough (n=2) to contribute a large coefficient of variation. No gender difference in exposure to test substances was noted. Maximum plasma concentration was reached at 0.5 hr for valsartan and HCTZ and at 2 hr for amlodipine. No tendency for accumulation was detected between day 1 and week 11 for either sex. Based on dose normalized AUC values, exposures to the individual drug components increased with increase in dose but were not dose proportional. There was a 52% increase in mean valsartan Cmax for both sexes and 54% increase in mean valsartan AUC for males (no increase for females) when co-administered with HCTZ and amlodipine. This increase is lower than the total variability of valsartan exposure and is considered clinically not relevant. Thus, it is concluded that exposure to valsartan, HCTZ and amlodipine was the same whether or not the compounds were administered together, suggesting no effect of one on the absorption and disposition of the other (Table 3.1.1.6).

TABLE 3.1.1.6
13 WEEK TOXICITY STUDY IN RATS
MEAN TOXICOKINETIC PARAMETERS FOR VALSARTAN IN RAT PLASMA

Time (h)	Group 2 Males	Females	Group 3 Males	Females	Group 4 Males	Females	Group 5 Males	Females
	Day 1							
t_{max}	0.500	0.500	0.500	0.500	1.00	0.500	1.00	0.500
C_{max}	2310	1630	5870	5600	22300	10700	9530	8350
C_{max}/dose	289	204	183	175	348	167	149	130
AUC_{0-24h}	10200	6540	21100	48200	90500	46600	33600	41900
AUC_{0-24h}/dose	1280	817	660	1510	1410	729	525	654
	Week 11							
t_{max}	0.500	0.500	0.500	0.500	0.500	0.500	0.500	0.500
C_{max}	2000	2540	6380	7030	13500	8250	8880	5410
C_{max}/dose	250	318	199	220	211	129	139	84.5
AUC_{0-24h}	6370	4940	14500	24500	70200	35100	45700	38700
AUC_{0-24h}/dose	796	618	452	765	1100	549	714	604

MEAN TOXICOKINETIC PARAMETERS FOR HCTZ IN RAT PLASMA

Time (h)	Group 2 Males	Females	Group 3 Males	Females	Group 4 Males	Females	Group 6 Males	Females
	Day 1							
t_{max}	0.500	2.00	1.00	0.500	1.00	2.00	0.500	0.500
C_{max}	145	166	489	440	880	1160	951	1550
C_{max}/dose	116	133	97.8	88.0	88.0	116	95.1	155
AUC_{0-24h}	717	925	2770	2930	7070	6910	5270	6350
AUC_{0-24h}/dose	573	740	554	585	707	691	527	635
	Week 11							
t_{max}	0.500	0.500	0.500	0.500	2.00	0.500	0.500	0.500
C_{max}	200	221	672	893	1800	1130	1220	1220
C_{max}/dose	160	177	134	179	180	113	122	122
AUC_{0-24h}	888	939	3090	3590	10300	6870	6100	5640
AUC_{0-24h}/dose	710	751	618	718	1030	687	610	564

MEAN TOXICOKINETIC PARAMETERS FOR AMLODIPINE IN RAT PLASMA

Time (h)	Group 2 Males	Females	Group 3 Males	Females	Group 4 Males	Females	Group 7 Males	Females
	Day 1							
t_{max}	2.00	2.00	1.00	2.00	0.500	1.00	1.00	0.500
C_{max}	3.42	4.88	15.7	25.6	33.4	47.4	47.0	95.2
C_{max}/dose	6.84	9.76	7.85	12.8	8.35	11.9	11.8	23.8
AUC_{0-24h}	25.2	40.3	155	205	234	367	279	454
AUC_{0-24h}/dose	50.5	80.6	77.4	102	58.5	91.9	69.8	114
	Week 11							
t_{max}	2.00	2.00	0.500	2.00	2.00	2.00	1.00	1.00
C_{max}	4.75	6.82	35.2	48.7	68.1	98.2	114	104
C_{max}/dose	9.50	13.6	17.6	24.4	17.0	24.6	28.5	26.0
AUC_{0-24h}	40.9	65.6	368	460	802	817	931	1100
AUC_{0-24h}/dose	81.8	131	184	230	200	204	233	275

t_{max} is expressed in hours, C_{max} in ng/mL, C_{max}/dose in (ng/mL)/(mg/kg/day), AUC_{0-24h} in (ng.h/mL) and AUC_{0-24h}/dose in (ng.h/mL)/(mg/kg/day)

Group 2: Low combination: 8:1.25:0.5 mg/kg/day (valsartan: hydrochlorthiazide: amlodipine) Group 3: Mid combination: 32:5:2 mg/kg/day (valsartan: hydrochlorthiazide: amlodipine) Group 4: High combination: 64:10: 4 mg/kg/day (valsartan: hydrochlorthiazide: amlodipine) Group 7: High amlodipine: 4 mg/kg/day amlodipine

4.0. OVERALL SUMMARY AND EVALUATION

VEA489 (Exforge® HCT) is a fixed dose combination of valsartan, hydrochlorothiazide (HCTZ) and amlodipine besylate. Valsartan is a non-peptidic, orally effective, specific antagonist of angiotensin II, active at the AT-1 receptor. It was developed by Novartis and was approved in 1996 for the treatment of essential hypertension (Diovan®, NDA 20,665). Hydrochlorothiazide, a diuretic, has been approved for the treatment of hypertension since 1959. Racemic amlodipine is a dihydropyridine calcium channel antagonist. It was developed by Pfizer and was approved in 1992 as the besylate salt for the treatment of hypertension, chronic stable angina and vasospastic angina (Norvasc®, NDA 19,787). Because of their different modes of action, the combination of these drugs is expected to result in an additive or synergistic antihypertensive effect when compared to single drug treatment. The only nonclinical study performed with a valsartan:HCTZ:amlodipine combination is a single 13 week toxicity study in Wistar-Hannover rats. In this study, the drugs were administered in a ratio of 16:2.5:1 (valsartan: HCTZ: amlodipine) on a weight basis.

The oral administration of valsartan and HCTZ either alone or in combination with amlodipine resulted in 6 deaths, none of which were attributed to drug treatment. Dose-dependent decreases in mean body weight gain relative to concurrent control were noted for both sexes with all dose combinations for the entire duration of the study. A decrease in erythroid parameters relative to control was noted for both sexes dosed with the mid or high dose combination or valsartan alone. Hyperplasia of the juxtaglomerular apparatus along with a moderate (<2-fold) increase in BUN was noted in both sexes at VEA489 doses of 32:5:2 or more mg/kg/day and with valsartan alone. Focal erosions of the glandular stomach were noted in males treated with valsartan alone or in combination with HCTZ and amlodipine at 32:5:2 or more mg/kg/day. None of these effects were noted in recovery group animals. The VEA489 NOAEL was determined to be 8:1.25:0.5 mg/kg/day.

Exposure to valsartan, HCTZ and amlodipine was the same whether or not the compounds were administered together, suggesting no effect of one on the absorption and disposition of the other. No tendency for accumulation was detected between day 1 and week 11 for either sex. Based on dose normalized AUC values, exposures to the individual drug components increased with increase in dose but were not dose proportional. The NOAEL exposures in rats for valsartan and amlodipine were only 0.06 to 0.13 times (based on AUC values) the exposure in humans dosed with 320:25:10 mg (valsartan:HCTZ:amlodipine)/day, the maximum recommended human dose (MRHD), indicating the absence of a safety margin for humans (Table 4.1).

TABLE 4.1
HUMAN VEA489 EXPOSURE MULTIPLES IN 13 WEEK TOXICITY STUDY IN RATS

Species	NOAEL[a] (mg/kg)	Gender	AUC_{0-24h} (ng·h/ml)[b]	C_{max} (ng/ml)[b]	Exposure multiples based on	
					AUC_{0-24h}	C_{max}
Valsartan	8	male	6370	2000	0.08	0.19
		female	4940	2540	0.06	0.24
HCTZ	1.25	male	888	200	0.45	0.88
		female	939	221	0.48	0.98
Amlodipine	0.5	male	40.9	4.75	0.08	0.18
		female	65.6	6.82	0.13	0.27

a: No-Observed-Adverse-Effect-Level, b: week 11
Valsartan, HCTZ and amlodipine exposure multiples were based on the human $AUC_{0-\infty}$ = 82687, 1969, 504.7 ng·h/ml and C_{max} = 1077, 226.3, 25.7 ng/ml, respectively, after 17 oral doses of 320:25:10 mg (valsartan:HCTZ:amlodipine) to male and female healthy subjects (Study #VEA489A2104)

Evaluation

Toxicities associated with the valsartan/HCTZ/amlodipine combinations (hyperplasia of the juxtaglomerular apparatus in the kidney, focal erosions of the stomach and decreased erythroid parameters) were all observed with valsartan alone, although the effects of the combination appeared to be somewhat greater with the combined administration than with valsartan, HCTZ or amlodipine alone.

Exposure to valsartan, HCTZ and amlodipine at the NOAEL dose in rats was far lower than exposure in humans (0.06 to 0.48 times, based on AUC values). In spite of this enhancement of toxicity and a low NOAEL for erosion in the stomach, decrease in body weight and erythroid parameters in rats, the target organ toxicities are monitorable, reversible and attributable to the effects of the individual components of the combination, which have been used, often concomitantly, to treat hypertensive patients since the approval of valsartan for this indication in 1996.

Recommendations on Labeling: See page 6

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