CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-314

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Priority or Standard	Standard
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Reviewer Name(s)	Salma Lemtouni, Efficacy Reviewer Ququan Liu, Statistical Reviewer Shona Pendse, Safety Reviewer
Review Completion Date	2/28/09
Established Name	valsartan/HCTZ/amlodipine
(Proposed) Trade Name	Exforge HCT
Therapeutic Class	Combination therapy
Applicant	Novartis Pharmaceuticals
Formulation(s)	Oral tablets
Dosing Regimen	Once daily
Indication(s)	Treatment of hypertension
Intended Population(s)	Adult hypertensives

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical and statistical perspective we recommend that Exforge HCT, the triple combination of valsartan, amlodipine, and hydrochlorothiazide, be approved for the treatment of hypertension in adults.

The triple combination was shown to be significantly more effective than any of the double combinations, and relatively safe in comparison to the double combinations as well. One thing to keep in mind is that the generalizability of the findings from this study may be limited. This is due to the fact that the inclusion/exclusion criteria with regard to hypertension severity, responsiveness to antihypertensive drugs, and co-morbidities might have led to a population that would most respond to the anti-hypertensive effect of the triple combination with few adverse events as observed here. It is not known whether African Americans or subjects who are older and/or have concomitant cardiac conditions, all of whom were under-represented in the study population, would benefit or exhibit a benefit to risk profile as favorable as that observed in this study. In our opinion, the label should include language regarding the under-representation of these sub-populations.

1.2 Risk Benefit Assessment

The triple combination was significantly more effective that any of the double combinations, and also had an acceptable safety profile. Thus, the overall risk benefit ratio appears to be favorable in the study population.

1.3 Recommendations for Postmarket Risk Management Activities

Exforge HCT does not have any unusual risks for which a postmarket risk management plan would be necessary. However, the use of this drug in elderly subjects who are often taking other medications and whose kidney function is likely to be decreased as a result of advanced age and cardiovascular disease should done with caution.

1.4 Recommendations for Postmarket Studies/Clinical Trials

We would recommend, but are not requiring, a study assessing the response of various subgroups such as African Americans, who are under-represented in the study and yet make up a substantial portion of the hypertensive population.

2 Introduction and Regulatory Background

2.1 Product Information

Exforge HCT film-coated tablets are a fixed combination product consisting of three well known and available drug substances: amlodipine as the besylate salt, valsartan and hydrochlorothiazide (HCT). Amlodipine is a dihydropyridine calcium channel blocker, valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype and hydrochlorothiazide, USP is a thiazide diuretic.

The tablets were formulated in five (5) strengths for oral administration with a combination of amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free base with 160 mg or 320 mg of valsartan and 12.5 mg or 25 mg of hydrochlorothiazide providing for the following available combinations: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg and 10/320/25 mg.

2.2 Tables of Currently Available Treatments for Proposed Indications

Many drugs are approved for the treatment of hypertension. The agents which are relevant to the discussion of Exforge HCT include calcium channel blockers, diuretics, and drugs which work through inhibition of the renin-angiotensin-aldosterone system (RAAS). RAAS inhibitors approved for hypertension include angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone receptor antagonists (eplerenone, spironolactone).

2.3 Availability of Proposed Active Ingredient in the United States

All of the individual components of Exforge HCT (valsartan, amlodipine, and hydrochlorothiazide) are approved products and thus are widely available in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

The major safety concerns specific to this product are those of hypotension and edema, both of which are covered in the safety portion of this review (Section 7).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Prior to the initiation of clinical studies, the sponsor had met with the US Food and Drug Administration (FDA) to solicit agreement on the overall development program. A Type B meeting was held with the FDA on October 13, 2004 regarding the development of a fixed-dose triple combination of valsartan, HCTZ, and amlodipine. A Special Protocol Assessment was submitted to the FDA on September 15, 2005, and an agreement was reached with the FDA such that one adequate and well-controlled [Study VEA A2302] would serve as the primary source of

efficacy data and the primary basis for approval. On May 9, 2007 Novartis conducted a pre-submission meeting with the FDA to discuss the intended submission plan.

2.6 Other Relevant Background Information

2.6.1 Adverse events specified in the labels of the two approved combinations

Exforge (valsartan/amlodipine)
Discontinuation due to side effects occurred in 1.8% of the Exforge-treated patients and 2.1% in the placebo-treated group. The most common reasons for discontinuation of therapy with Exforge were peripheral edema (0.4%), and vertigo (0.2%).
Peripheral edema, nasopharyngitis, upper respiratory tract infection and dizziness were observed more commonly with Exforge compared to placebo.

Diovan HCT (valsartan/HCTZ)
Discontinuation due to adverse events on valsartan/HCTZ was observed in 3.6% of the patients in controlled clinical trials compared with 4.3% of placebo subjects. The most common reasons for discontinuation were headache, fatigue and dizziness. Dizziness, viral infection, fatigue, pharyngitis, coughing, and diarrhea were observed more commonly with Diovan HCT compared to placebo. Dizziness was observed in patients treated with valsartan/HCTZ in dose-related fashion.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

We assessed the quality and integrity of the **sponsor's submission by examining both the Case** Report Forms as well as the SAS data sets. In general we found the Case Report Forms to be complete and accurately represented in the SAS data sets.

3.2 Compliance with Good Clinical Practices

The sponsor claims that all studies were conducted in full compliance with Good Clinical **Practice. All of the current sponsor's studies** were closely monitored by its personnel or a contract organization for compliance to the protocol and the procedures described in it. They were also monitored to insure the safety of the patients and the ethical procedures required by the following directives:

1. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).

2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.

3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning informed patient consent and Institutional Review Board approval.

We have not found any reason to believe **that the sponsor's claims are untrue.**

3.3 Financial Disclosures

The sponsor provided a FDA Form 3454 financial disclosure certification for the investigators in Study VEA489A2302, the pivotal efficacy study, as well as all of the supporting studies. Response rates were 100% in all studies except for Study 489A2302, the pivotal study, which had a response rate of 99.6% for the US centers (2 centers out of a total of 521 US centers did not respond). Of the returned forms only one identified a financial interest. This was an investigator from Study [redacted] **who reported "Honoraria and travel expenses for education activities" exceeding $25,000.** b(4)

Reviewing the remainder of the financial disclosure information, we found that all of the investigators from all of the centers in Slovakia reported having financial interest. When we emailed the sponsor inquiring as to the nature of this financial interest, they replied with the statement that none of these Slovakian investigators were in the pivotal efficacy study, but were only involved in Study VAA489A2401, one of the supporting studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Amlodipine besylate is a white to pale yellow crystalline powder that is slightly soluble in water and sparingly soluble in ethanol. The sponsor currently purchases amlodipine besylate from **three drug substance suppliers:** [redacted] b(4)
([redacted] to manufacture the VEA489 tablets. The sponsors performed comparison studies of the assorted amlodipine suppliers to demonstrate that material received from any supplier would be suitable for the manufacture of VEA489 film-coated tablets. All the suppliers have Drug Master Files on file with the Agency. Valsartan (Novartis) is a white, microcrystalline and slightly bitter tasting powder described in the USP, which has a melting

range of 105-110°C (decomposition), a median particle size of less than —, and a bulk density of less than —. Hydrochlorothiazide is a white, crystalline powder, slightly soluble in water, freely soluble in sodium hydroxide solution and sparingly soluble in methanol, which is described in both the USP and the European Pharmacopoeia. The sponsor currently purchases hydrochlorothiazide from two drug substance suppliers: — The commercial material is — by Novartis prior to usage in the manufacture the VEA489 tablets. A comparison study of the HCT suppliers was completed to demonstrate that material received from any supplier would be suitable for the manufacture of VEA489 film-coated tablets . All the suppliers have Drug Master Files on file with the Agency. Stability data for the three active components, amlodipine besylate, valsartan and hydrochlorothiazide (HCT) intermixed by themselves with no other additives has not been obtained. However, compatibility of the three active components was evaluated by intermixing powdered 5 mg amlodipine, 320 mg valsartan, and 12.5 mg HCT products and storing them for 6 weeks at 50 °C and 50 °C/75%RH conditions. The results indicated that the drug substances were compatible at 50 °C, but not at 50 °C/75%RH. b(4)

The objective of formulation development for the combination drug product was to generate an immediate release tablet combination product that was the bioequivalent to the clinical free forms of Diovan commercial tablets, hydrochlorothiazide clinical service form (CSF) capsules and amlodipine CSF capsules.

As detailed in the CMC review, there were numerous deficiencies that need to be addressed including providing additional manufacturing information, stability data, and drug product specifications.

— The sponsor was also asked to submit the revised Novartis Test Specification for Amlodipine Besylate from —. b(4)

Please see Dr. Soldatova's review for full details of CMC review.

4.2 Clinical Microbiology

Clinical Microbiology evaluation is not applicable for this product given that it is an oral formulation.

4.3 Preclinical Pharmacology/Toxicology

A 13 week oral (gavage) repeat dose toxicity study, followed by a 4 week recovery period, was performed in Wistar-Hannover rats, which showed the NOAEL to be 8:1.25:0.5 mg/kg/day of valsartan:HCTZ:amlodipine, respectively. There were 6 deaths in this study, none of which were attributed to drug treatment. Dose-dependent decreases in mean body weight gain relative to controls were observed. Decrease in erythroid parameters relative to control was noted 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 observed at doses of 32:5:2 or more (valsartan:HCTZ:amlodipine 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.

Exposure to valsartan, HCTZ and amlodipine was the same regardless of whether or not they were administered together, suggesting no effect of one on the absorption and disposition of the other. No accumulation was detected up to week 11. 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) – which is an** inadequate safety margin for humans. However, given that the target organ toxicities are monitorable and can be attributed to the individual components, all of which are approved and have been used together in current practice, the combination product can be used in humans.

Please refer to Dr. Jagadeesh's review for full details of Preclinical Pharmacology/Toxicology review findings.

4.4 Clinical Pharmacology

Please refer to Dr. Menon-Andersen's Clinical Pharmacology review for full discussion of review findings, summarized below.

Two studies were conducted which showed bioequivalence 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).

The drug interaction study (study number VEA489A2104) showed no clinically significant pharmacokinetic drug interaction between the components (Valsartan, Hydrochlorothiazide, and Amlodipine) of Exforge HCT.

The food effect study (study number VEA489A2310) revealed no effects of food on the pharmacokinetics of Exforge HCT.

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.

4.4.1 Mechanism of Action

Valsartan selectively blocks type 1 angiotensin II (AT_1) receptors and thereby results in vasodilatation, down-regulation of sympathetic adrenergic activity, and pro-natriuretic and pro-diuretic effects in the kidney through inhibition of the effects of angiotensin II and angiotensin II stimulation of aldosterone secretion.

Hydrochlorothiazide is a thiazide diuretic, which inhibits Na/Cl reabsorption from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive luminal NaCl symporter.

Amlodipine is a dihydropyridine calcium channel blocker. It acts via the selective inhibition of the transmembrane influx of calcium ions into muscle (cardiac muscle to a greater extent than vascular smooth muscle).

4.4.2 Pharmacodynamics

No pharmacodynamic studies were conducted with the triple combination product.

4.4.3 Pharmacokinetics

No pharmacokinetic or ADME studies have been conducted with the triple combination product.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Sponsor's table of completed trials or sources of data

Source of data	Details
Dose-selection trials	None
Controlled efficacy trials	1 double-blind active-controlled phase III trial of the valsartan/HCTZ /amlodipine combination (primary): VEA A2302
Uncontrolled efficacy trials	1 open-label uncontrolled trial of the valsartan/HCTZ /amlodipine combination (secondary): VEA ABR01
Long-term tolerability and efficacy trials	1 long-term open-label trial designed to evaluate the long-term tolerability and efficacy of amlodipine/valsartan with optional addition of HCTZ (supportive): VAA A2201E1
Other trials containing safety data for the valsartan/HCTZ/amlodipine triple combination	6 trials designed to evaluate various regimens of either the amlodipine/valsartan, valsartan/HCTZ, or amlodipine/HCTZ dual combinations with the optional addition of the third component (supportive): VAA A2401, VAA A2402, VAA A2403, VAH BUS04, VAH BDE13E1, VAH B2406E1

[Source: Table 1-1, Summary of Clinical Efficacy, Novartis Pharmaceuticals]

5.2 Review Strategy

We focused on the pivotal study for the review of efficacy. For the safety review, we focused on the pivotal study but also looked at the data for the entire safety population, including the long-term open-label trial VAA A2201E1 and the uncontrolled supportive study for efficacy, VEA ABR01, the safety data of which we found to be consistent with that of the pivotal study.

5.3 Discussion of Individual Studies/Clinical Trials

We focused on the major pivotal study for both the efficacy and safety analyses, which are discussed in sections 6 and 7, respectively.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the treatment of hypertension in adults.

6.1.1 Methods

6.1.1.1 Overall Summary of Methods

The study reviewed here (conducted under protocol VEA489a2302) is the pivotal study of NDA 22314. This application is seeking approval for the triple combination of valsartan, amlodipine and hydrochlorothiazide (V/A/H) for the treatment (not as an initial therapy) of hypertension. In this study, the triple combination was compared to the three double combinations (V/H, V/A, A/H) of the individual components. Two of the double components used for comparison, V/H and V/A (EXFORGE) are approved and indicated for the treatment of hypertension.

"An 8-week, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of the combination of valsartan/HCTZ/amlodipine compared to valsartan/HCTZ, valsartan/amlodipine, and HCTZ/amlodipine in patients with moderate to severe Hypertension"

This study was initiated in May of 2006 and completed in August of 2007 It was conducted in 15 countries from North and South America, Western and Eastern Europe and Asia. More than 50% of the study population was randomized in North America.

The primary objective of this study was to demonstrate that the triple combination of V/H/A is superior to all double combinations: V/A, V/H and V/A in lowering mean sitting diastolic and/or systolic blood pressure in patients with moderate to severe hypertension.

Secondary objectives include:
--demonstrating that blood pressure control rates on the triple combination are superior to blood pressure control rates on any double combination; with blood pressure control defined for different endpoints as 1) mean sitting systolic blood pressure (MSSBP) and mean sitting diastolic blood pressure (MSDBP) < 140/90 mmHg, 2) MSDBP <90 mmHg, and 3) MSSBP < 140 mmHg;
--demonstrating that blood pressure responder rates on the triple combination are better than those on the double combinations; with blood pressure response defined for different endpoints as 1) MSDBP < 90 mmHg and/or a change from baseline >= 10 mmHg, and 2) MSSBP < 140 mmHg and/or a change from baseline >= 15 mmHg;

--demonstrating a decrease in 24-hour mean ambulatory diastolic and systolic blood pressure on the triple combination compared to any double combination;
-- evaluating the safety and tolerability of the triple combination in comparison to the double combinations;
--determining whether there is pharmacokinetic drug interaction at steady state by comparing the plasma drug levels of the individual components when taken in a triple combination compared to when taken in double combinations.

This is a factorial, randomized double blind study in which at Visit 3 (day 1), patients who were eligible to participate in the placebo run-in-period and who qualified after being withdrawn from their anti-hypertensive medication were to be randomized to four study drug combinations: one triple combination and three double combinations of valsartan, HCTZ and amlodipine.
Eligibility for enrollment was based on patients' office blood pressure and the number of antihypertensive medications being taken at the time of screening. A total of 4500 subjects with moderate to severe hypertension were to be screened; and 2252 (506 per treatment group) patients were expected to be randomized. Subjects meeting the eligibility criteria were to have their antihypertensive therapy withdrawn and be entered into the single-blind placebo run-in-period. Patients taking antihypertensive medication that requires gradual withdrawal were to be down-titrated prior to entering the placebo run-in period. After one week on placebo, patients were assessed for blood pressure eligibility before randomization, and if they were found not eligible, they were maintained on placebo for another two to three weeks after which they were either randomized if they were eligible or discontinued from the study.
A 24-hour ambulatory blood pressure monitoring (ABPM) sub-study was to be conducted in 670 randomized patients. Patients participating in the ABPM sub-study were to return to the study site one day before Visit 3 and Visit 8 to be instrumented with the ABPM device if blood pressure eligibility criteria were met.

6.1.1.2 Blood pressure inclusion criteria:

To be included were subjects 18 to 85 years of age who met specific BP criteria at Visit 3: MSDBP $\geq$ 110 mmHg and < 120 mmHg, and MSSBP $\geq$ 145 mmHg and < 200 mmHg, or MSDBP $\geq$ 100 mmHg and < 110 mmHg and MSSBP $\geq$ 180 mmHg and < 200 mmHg. At any time during the study, if a patient had a systolic blood pressure > 200 mm Hg and/ or a diastolic blood pressure > 120 mm Hg, the patient was to be discontinued from the study.
Patient who were eligible were randomized in a ratio of 1:1:1:1 to four combination arms: one triple (V/H/A) and three double (V/H, V/A, A/H) combinations. Subjects were initiated on combinations of lower doses (valsartan: 160 mg; HCTZ: 12.5 mg; and amlodipine: 5 mg) for two weeks before they were force-titrated to and maintained on combinations of higher doses (valsartan: 320 mg; HCTZ: 25 mg; amlodipine: 10 mg) for at least six weeks. For subjects who were randomized to the triple combination, the dose of the amlodipine component was 0 mg for the first week, but this was escalated to 5 mg in the second week. The total duration of the study was to be 9 to 13 weeks, and downward dose adjustment of the study drugs was not permitted.

6.1.1.3 Exclusion criteria:

The exclusion criteria were numerous. Subjects were excluded from the study if not able to discontinue their antihypertensive medication safely for one to five weeks; if at any time between one week and four weeks of treatment with placebo their MSSBP $\geq$ 180 mmHg and MSDBP < 100 mmHg; if at visit 1: MSSBP $\geq$ 180 and MSDBP $\geq$ 110 mmHg while on two antihypertensive drugs, MSDBP $\geq$ 90 mmHg and < 110 mmHg, and/or MSSBP $\geq$ 140 mmHg and < 180 mmHg while on three or more antihypertensive drugs, or if they were on four or more antihypertensive drugs; if they were pregnant, nursing or of child-bearing potential without reliable contraception; if they have known moderate or malignant retinopathy, history of hypertensive encephalopathy, cerebrovascular accident or TIA; if they have angina pectoris, history of MI or any type of revascularization procedure, HF requiring treatment, second or third degree heart block, concurrent potentially symptomatic and/or life-threatening arrhythmia, clinically significant valvular heart disease; or evidence of a secondary form of hypertension; if they need administration of any agent indicated for the treatment of hypertension after Visit 1; if they have **DM that per investigator's judgment is not well** controlled; any surgical or medical condition that might significantly alter the pharmacokinetic of the study drug; any history of pancreatic injury or pancreatitis or evidence of impaired pancreatic function within one year of Visit 1; evidence of hepatic disease defined as AST or ALT > 2 x ULN at Visit 1, history of hepatic encephalopathy, history of esophageal varices or history of portocaval shunt; evidence of renal impairment determined by serum creatinine $\geq$ 1.5 x ULN, history of dialysis or history of nephrotic syndrome; if their serum sodium and potassium levels are less than 132 mEq/L and 3.2 mEq/L respectively at Visit 2; if they have **volume depletion based on the investigator's** judgment; history of clinically significant allergies including asthma and multiple drug allergies; history of gouty arthritis or autoimmune diseases including systemic lupus erythematosus; history any chronic inflammatory condition necessitating chronic anti-inflammatory therapy; history of malignancy of any organ system within the past 5 years with the exception of localized basal cell carcinoma of the skin; history of drug or alcohol abuse within the last two years; and if they are currently taking prohibited concomitant medications.

6.1.1.4 Withdrawal Criteria:

To be withdrawn from the study were patients who were found to have MSSBP $\geq$ 200 mmHg and/or MSDBP $\geq$ 120 mmHg at Visit 3 through Visit 5; MSSBP $\geq$ 180 mmHg and/or MSDBP $\geq$ 110 mmHg post Visit 5 through to end of study; or signs and symptoms of hypotension with a MSSBP < 100 mmHg or MSDBP < 60 mmHg.

Figure 1: Schema of study design

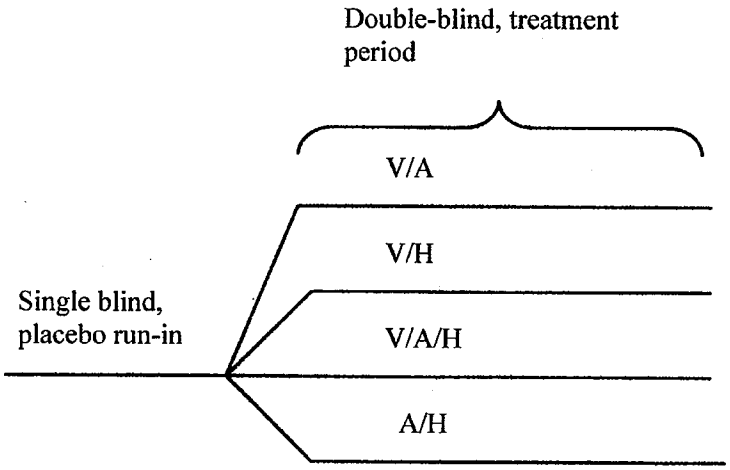


Table 2: Study outline and study medication dosing

Phase	Pre-randomization		Study Drug Treatment					
Period	Single-blind run-in		Double-blind treatment					
Duration	(1-2 W)	(1-3 W)	(8 weeks)					
Visit	1	2	3	4	5	6	7	8
Week	-4	-2	1	2	3	5	7	9
Treatment	Placebo		**Randomization**					
			Dose of V, H and A (V/H/A) in the different combinations					
			First week	**Second week**	**Week 3 through end of treatment period**			
			0/12.5/5	0/12.5/5	0/25/10			
			160/12.5/0	160/12.5/0	320/25/0			
			160/0/5	160/0/5	320/0/10			
			160/12.5/0	160/12.5/5	320/25/10			
Patients on an antihypertensive medication at Visit 1 that requires gradual withdrawal will undergo a one week washout period prior to the start of the single-blind placebo run-in period								

Table 3: Study procedures and assessment schedule

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	**-4 to -3**	**-3 to -1**	**1**	**2**	**3**	**5**	**7**	**9**
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X	X					
Screening Log	X							
Medical History/Background Info	X							

Visit	1	2	3	4	5	6	7	8
Week	-4 to -3	-3 to -1	1	2	3	5	7	9
Physical Examination – Complete	X							
Physical Examination – Interim		X	X	X	X	X	X	X
Weight and Height	X		X					X
Blood Pressure and Pulse	X	X	X	X	X	X	X	X
Instruct/Review Home BP Monitoring	X	X	X	X	X	X	X	
Review Patient BP Diary		X	X	X	X	X	X	X
24-hour ABPM (in subset of patients)			X X					X X
ECG	X							
Hematology, Chemistry	X		X					X
Chemistry					X	X		
Pharmacokinetics						X		X
Serum Pregnancy Test	X							X
Urine Pregnancy Test			X			X		
Prior/Concomitant Medications/ Significant Non-Drug Therapies	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Randomization			X					
Dispense Study Medication	X	X	X	X	X	X	X	
Drug Accountability		X	X	X	X	X	X	X
Study Completion/Early Termination								X

6.1.1.5 Blood pressure measurements

Three sitting (at two-minute intervals) and one standing (from a sitting position) blood pressure measurements were to be performed at trough (23 to 26 hours post dose) and at the same time of day using an [redacted] blood pressure monitor at each visit. b(4)

In a subpopulation of 670 randomized patients twenty-four hour ambulatory blood pressure monitoring was to be conducted at baseline and at Visit 8 using an ABPM device.

6.1.1.6 Statistical Methodology

6.1.1.6.1 Sample size and populations for analyses

Sample size was calculated based on the following: 10% drop-out rate; 90% power to achieve statistical significance for the effect (measured as change from baseline) of the triple combination in comparison to the double combinations at the two-sided significance level of 0.025; a difference of 2 mmHg in MSDBP for each pair-wise comparison and a common standard deviation of 8 mmHg for all treatment groups; and a difference of 3.5 mmHg in MSSBP for each pair-wise comparison and a common standard deviation of 14 mmHg for all treatment groups.

The primary efficacy population is the ITT population which consists of all randomized patients who had a baseline and at least one post-baseline measurement of the primary or secondary

efficacy variables. Data from Site 556 were excluded from efficacy analyses due critical GCP findings that resulted in the closure of the site.

The safety population included all subjects who were randomized and received at least one dose of the double-blind study drug.

The ABPM population included all subjects who participated in the ABPM sub-study and had valid baseline and post-baseline ABP reading.
PK population included all subjects with at least one evaluable PK measurement.

6.1.1.6.2 Efficacy variables and populations to be tested

6.1.1.6.2.1 Primary efficacy variables

The primary efficacy variables are the changes from baseline in MSDBP and MSSBP.

$H0_1$ MSDBP: effect of triple combination = effect of at least one of the double combination

$H0_1$ MSSBP: effect of triple combination = effect of at least one of the double combination

Ha_1 MSDBP: effect of triple combination ≠ effect of each and every double combination on MSDBP

Ha_1 MSSBP: effect of triple combination ≠ effect of each and every double combination on MSSBP

Each Ha_1 hypothesis has three hypotheses embedded in it: comparison of the triple combination (V/H/A) to each of the three double combinations (V/A, V/H and A/H) with regard to the effect on MSDBP and MSSBP. The null hypothesis of no effect is met if the triple combination fails to be superior to any of the double combinations; and this is rejected when the triple combination is found to be superior to each and every double combination. For each set of hypotheses, the intersection-union test (IUT) was applied to the comparisons between the triple combination and each of the three pairwise combinations. The efficacy objective is achieved if superiority is achieved for either one or both primary efficacy variables (MSDBP, MSSBP). Hochberg's multiple-testing step-up procedure was used to control the overall type I error rate at 0.05 for the above two sets of hypothesis tests. Superiority is satisfied at the significance level of 0.05 if the triple combination is shown to be superior with regard to both primary efficacy variables, and at the level of 0.025 if it was shown to be superior with regard to only one of the primary efficacy variables.

An analysis of covariance (ANCOVA) model was used in the primary analyses for the ITT population. The dependent variable of the model was the change from baseline to endpoint in MSDBP/MSSBP. The explanatory variables of the model included treatment and region as factors, and baseline MSDBP/MSSBP as a covariate.

6.1.1.6.2.2 Secondary efficacy analyses

Secondary efficacy variable include:

- MSSBP/MSDBP control rate (MSSBP/MSDBP < 140/90 mmHg).
- MSDBP control rate (MSDBP < 90 mmHg).
- MSSBP control rate (MSSBP < 140 mmHg).
- **MSDBP responder rate (MSDBP < 90 mmHg or** □10 mmHg reduction from baseline).
- MSSBP responder rate **(MSSBP < 140 mmHg or** □15 mmHg reduction from baseline).
- Change from baseline at endpoint in post-dosing 24-hour mean ambulatory diastolic blood pressure (ADBP)
- Change from baseline at endpoint in post-dosing 24-hour mean ambulatory systolic blood pressure (ASBP)
- Change from baseline at endpoint in daytime mean ambulatory diastolic blood pressure (ADBP)
- Change from baseline at endpoint in daytime mean ambulatory systolic blood pressure (ASBP)
- Change from baseline at endpoint in nighttime mean ambulatory diastolic blood pressure (ADBP)
- Change from baseline at endpoint in nighttime mean ambulatory systolic blood pressure (ASBP)

To assess and quantify differences with respect to control and responder rates, similar pair-wise comparisons specified for the primary efficacy variable were to be performed using a logistic regression model.

The effect on the 24-hour mean ambulatory blood pressure was to be evaluated through assessment of the change from baseline mean to post-dosing time point (hours 1 to 24) hourly means. The change from baseline at each time point in post-dosing 24-hour mean diastolic blood pressure and systolic blood pressure was to be analyzed using an ANCOVA model for repeated measures with treatment, region, and post-dosing hour as factors, and baseline 24-hour mean blood pressure as a covariate. The treatment difference between the triple combination and each double combination therapy was to be estimated with the least-square means and 95% confidence intervals. Change from baseline in daytime (> 6:00 AM to ≤ 10:00 PM) and nighttime (> 10:00 PM to ≤ 6:00 AM) ambulatory blood pressure means was to be evaluated using the same method described (above) for hourly ambulatory blood pressure means.

6.1.1.6.2.3 Handling of missing data

The last non-baseline observation was to be carried forward to impute for missing observations.

6.1.1.6.2.4 Safety

Safety of the triple combination was to be evaluated in comparison to the double combinations. Assessment of safety was based on the frequency of adverse events, notable laboratory abnormalities, and orthostatic hypotension with the latter defined as a decrease of at least 10

mmHg in diastolic blood pressure or 20 mmHg in systolic blood pressure when a patient moves from a sitting to a standing position.

6.1.2 Demographics

6.1.2.1 Enrollment by country and analyses populations

Table 4: Number of subjects by country

Country	Frequency	Percent	Cumulative Frequency	Cumulative Percent
ARG	348	15.48	348	15.48
CAN	83	3.69	431	19.17
DNK	73	3.25	504	22.42
ECU	49	2.18	553	24.60
GBR	178	7.92	731	32.52
GRC	4	0.18	735	32.70
HKG	10	0.44	745	33.14
NOR	63	2.80	808	35.94
PER	57	2.54	865	38.48
PRT	4	0.18	869	38.66
RUS	210	9.34	1079	48.00
SWE	25	1.11	1104	49.11
TUR	40	1.78	1144	50.89
USA	1081	48.09	2225	98.98
VEN	23	1.02	2248	100.00

The findings above show that more than 50% of the study population was enrolled in North America (US (49%) and Canada 4%)).

Table 5: Analysis populations by treatment

	Val/HCTZ/Aml 320/25/10 mg N (%)	Val/HCTZ 320/25 mg N (%)	Val/Aml 320/10 mg N (%)	HCTZ/Aml 25/10 mg N (%)	Total N (%)
Enrolled population (ENR)					4285
Randomized population (RND)	583 (100.0)	559 (100.0)	568 (100.0)	561 (100.0)	2271 (100.0)
Intent-to-Treat population (ITT)	571 (97.9)	553 (98.9)	558 (98.2)	554 (98.8)	2236 (98.5)
Safety population (SAF)	582 (99.8)	559 (100.0)	566 (99.6)	561 (100.0)	2268 (99.9)
Per protocol population (PP)	471 (80.8)	449 (80.3)	469 (82.6)	443 (79.0)	1832 (80.7)
ABPM population (ABP)	67 (11.5)	69 (12.3)	71 (12.5)	76 (13.5)	283 (12.5)
PK population (PK)	536 (91.9)	520 (93.0)	524 (92.3)	520 (92.7)	2100 (92.5)

The ABPM population is less than half the size of the population planned.

6.1.2.2 Extent of Exposure

As can be seen in Table 20 in the Review of Safety (please refer to Table 20: Duration of exposure to study drug by treatment group in the confirmatory study), almost 90% of the study population was exposed to the study drug for at least seven weeks and about 41% were exposed to the study drug for 8 weeks or longer.

6.1.2.3 Baseline characteristics

Table 6: Demographics by treatment

	Val/HCTZ/Aml 320/25/10 mg N = 583	Val/HCTZ 320/25 mg N = 559	Val/Aml 320/10 mg N = 568	HCTZ/Aml 25/10 mg N = 561	Total N = 2271
Age (years) n	583	559	568	561	2271
Mean (SD)	53.3 (10.28)	53.1 (10.36)	52.8 (10.29)	53.6 (10.13)	53.2 (10.26)
Range	20-82	21-84	23-83	19-82	19-84
Age group (<65; ≥ 65)					
<65	501 (85.9%)	483 (86.4%)	492 (86.6%)	478 (85.2%)	1954 (86.0%)
≥ 65	82 (14.1%)	76 (13.6%)	76 (13.4%)	83 (14.8%)	317 (14.0%)
Age group (<75; ≥ 75)					
<75	570 (97.8%)	552 (98.7%)	554 (97.5%)	553 (98.6%)	2229 (98.2%)
≥ 75	13 (2.2%)	7 (1.3%)	14 (2.5%)	8 (1.4%)	42 (1.8%)
Sex					
Male	316 (54.2%)	303 (54.2%)	319 (56.2%)	317 (56.5%)	1255 55.3%)
Female	267 (45.8%)	256 (45.8%)	249 (43.8%)	244 (43.5%)	1016 (44.7%)
Race					
Caucasian	420 (72.0%)	412 (73.7%)	403 (71.0%)	392 (69.9%)	1627 (71.6%
Black	98 (16.8%)	93 (16.6%)	91 (16.0%)	107 (19.1%)	389 (17.1%)
Asian	4 (0.7%)	6 (1.1%)	10 (1.8%)	7 (1.2%)	27 (1.2%)
Native American	3 (0.5%)	3 (0.5%)	8 (1.4%)	4 (0.7%)	18 (0.8%)
Pacific Islander	2 (0.3%)	2 (0.4%)	1 (0.2%)	0 (0.0%)	5 (0.2%)
Other	56 (9.6%)	43 (7.7%)	55 (9.7%)	51 (9.1%)	205 (9.0%)
Body Mass Index (kg/m^2)					
n	581	554	565	557	2257
Mean (SD)	32.2 (6.91)	32.3 (6.95)	31.8 (6.41)	31.5 (6.07)	32.0 (6.60)
Range	20-78	18-83	19-60	16-57	16-83

The analysis above shows no difference in demographics between the treatment groups; that the majority of the study population is relatively young (< 65 years of age) and few (< 2%) were 75 years of age or older; and that almost three quarters (72%) of the study population were Caucasians.

Table 7: Summary of baseline characteristics by treatment

	Val/HCTZ/Aml 320/25/10 mg N = 583	Val/HCTZ 320/25 mg N = 559	Val/Aml 320/10 mg N = 568	HCTZ/Aml 25/10 mg N = 561	Total N = 2271
MSDBP (mmHg)					
n	583	559	568	561	2271
Mean (SD)	106.4 (5.08)	106.2 (5.07)	106.6 (5.14)	107.1 (5.14)	106.5 (5.12)
Range	93-119	96-119	86-119	98-120	86-120
MSSBP (mmHg)					
n	583	559	568	561	2271
Mean (SD)	169.6 (14.49)	169.5 (13.81)	169.6 (13.70)	170.8 (14.25)	169.9 (14.07)
Range	145-200	144-200	140-200	142-200	140-200
Standing DBP (mmHg)					
n	583	559	568	561	2271
Mean (SD)	108.5 (8.45)	108.6 (8.28)	108.1 (8.35)	108.7 (8.39)	108.5 (8.37)
Range	69-137	78-135	85-136	82-134	69-137
Standing SBP (mmHg)					
n	583	559	568	561	2271
Mean (SD)	169.1 (16.23)	169.8 (16.27)	168.3 (16.56)	169.3 (16.61)	169.1 (16.42)
Range	129-229	132-219	117-216	129-219	117-229
Sitting pulse (bpm)					
n	583	559	568	561	2271
Mean (SD)	77.5 (11.99)	77.3 (12.24)	77.1 (12.21)	78.0 (12.23)	77.5 (12.16)
Range	48-128	43-133	37-156	42-126	37-156
Standing pulse (bpm)					
n	583	559	568	561	2271
Mean (SD)	81.0 (12.46)	80.7 (12.51)	80.2 (13.23)	81.2 (12.46)	80.8 (12.66)
Range	50-124	45-125	41-159	49-130	41-159
Duration of hypertension (months)					
n	583	558	568	561	2270
Mean (SD)	99.8 (99.02)	107.9 (107.71)	106.2 (100.31)	107.5 (104.39)	105.3 (102.85)
Range	0-552	0-600	0-648	0-600	0-648
History of diabetes					
No	521 (89.4%)	499 (89.3%)	520 (91.5%)	515 (91.8%)	2055 (90.5%
Yes	62 (10.6%)	59 (10.6%)	48 (8.5%)	46 (8.2%)	215 (9.5%)

Except for the duration of hypertension which was shorter (by at least 6 months) in the group on the triple combination compared to groups on the double combinations, there are no differences between the treatment groups.

6.1.3 Subject Disposition

Table 8: Patient disposition by treatment (all randomized patients)

	Val/HCTZ/Aml 320/25/10 mg N=583	Val/HCTZ 320/25 mg N=559	Val/Aml 320/10 mg N=568	HCTZ/Aml 25/10 mg N=561	Total N=2271
Completed	522 (89.5)	506 (90.5)	526 (92.6)	506 (90.2)	2060 (90.7)
Discontinued	61 (10.5)	53 (9.5)	42 (7.4)	55 (9.8)	211 (9.3
Adverse event(s)	24 (4.1)	17 (3.0)	10 (1.8)	20 (3.6)	71 (3.1)
Subject withdrew consent	11 (1.9)	13 (2.3)	15 (2.6)	17 (3.0)	56 (2.5)
Lost to follow-up	8 (1.4)	11 (2.0)	10 (1.8)	6 (1.1)	35 (1.5)
Unsatisfactory therapeutic effect	4 (0.7)	6 (1.1)	0 (0.0)	7 (1.2)	17 (0.7)

Administrative problems	5 (0.9)	2 (0.4)	5 (0.9)	3 (0.5)	15 (0.7)
Protocol violation	9 (1.5)	1 (0.2)	2 (0.4)	2 (0.4)	14 (0.6)
Subject condition no longer requires study drug	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.1)
Abnormal laboratory value(s)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)

About 9% discontinued from the study and one third of the discontinuations were due to adverse events, over one third withdrew consent or was lost to follow-up, and the remaining was discontinued for lack of effect, administrative problems or protocol violation.

Table 9: Number of patients with protocol deviations leading to exclusion from per-protocol population

	Val/HCTZ/Aml 320/25/10 mg N=583	**Val/HCTZ 320/25 mg N=559**	**Val/Aml 320/10 mg N=568**	**HCTZ/Aml 25/10 mg N=561**
Total n (%) with ≥ 1 protocol deviation	78 (13.4)	74 (13.2)	72 (12.7)	88 (15.7)
Time of BP measurement < 20 or > 30 hours post last dose of study medication	42 (7.2)	38 (6.8)	34 (6.0)	47 (8.4)
Study drug interruption > 3 consecutive days prior to Visit 8/End of Study	17 (2.9)	11 (2.0)	12 (2.1)	18 (3.2)
NSAIDs and/or Cox-2 inhibitors taken ≤ 72 hours prior to Visits 3 or 8/End of Study	11 (1.9)	6 (1.1)	5 (0.9)	3 (0.5)
No post-baseline efficacy assessment	7 (1.2)	3 (0.5)	5 (0.9)	5 (0.9)
Use of antihypertensive medications (except for study medication) after Visit 3	6 (1.0)	2 (0.4)	0 (0.0)	6 (1.1)
Randomized patients with a MSDBP <95 mmHg at Visit 2	5 (0.9)	5 (0.9)	10 (1.8)	5 (0.9)
Critical GCP findings resulting in site closure	4 (0.7)	3 (0.5)	3 (0.5)	2 (0.4)
MSDBP < 100 mmHg at Visit 3	4 (0.7)	5 (0.9)	5 (0.9)	2 (0.4)
MSSBP ≥ 145 and <180 mmHg and a MSDBP ≥ 100 and < 110 and randomized without having a Visit 2	4 (0.7)	6 (1.1)	7 (1.2)	7 (1.2)
Randomized with MSSBP ≥ 140 mmHg and < 180 mmHg and/or MSDBP ≥ 90 and < 110 mmHg taking 3 or more antihypertensive medications at Visit 1	0 (0.0)	7 (1.3)	3 (0.5)	4 (0.7)

6.1.4 Analysis of Primary Endpoint(s)

Table 10: Change from baseline to endpoint in mean sitting BP (ITT population)

	N	Mean change from Baseline (SE)	95% CI for mean change	P-value
Diastolic BP				
Val/HCTZ/Aml 320/25/10 mg	571	-24.57 (0.395)	(-25.348, -23.797)	<0.0001 *
Val/HCTZ 320/25 mg	553	-19.40 (0.431)	(-20.250, -18.558)	<0.0001 *
Val/Aml 320/10 mg	558	-21.41 (0.394)	(-22.186, -20.639)	<0.0001 *
HCTZ/Aml 25/10 mg	554	-19.60 (0.407)	(-20.399, -18.801)	<0.0001 *
Systolic BP				
Val/HCTZ/Aml 320/25/10 mg	571	-39.37 (0.692)	(-40.725, -38.008)	<0.0001 *
Val/HCTZ 320/25 mg	553	-31.81 (0.739)	(-33.266, -30.362)	<0.0001 *

Val/Aml 320/10 mg	558	-33.37 (0.660)	(-34.668, -32.077)	<0.0001 *
HCTZ/Aml 25/10 mg	554	-31.87 (0.710)	(-33.264, -30.475)	<0.0001 *

All combinations reduced systolic and diastolic blood pressure significantly, but the triple combination did so to a greater extent than the double combinations.

Table 11: Comparison of change from baseline in mean sitting BP between treatments (ITT population)

	LSM change from baseline	LSM difference in change (SE)	p-value	Hochberg adjusted p-value
Diastolic BP				
Val/HCTZ/Aml 320/25/10	-24.74			<0.0001*
Val/HCTZ 320/25	-19.69	-5.05 (0.539)	<0.0001	
Val/Aml 320/10	-21.49	-3.25 (0.537)	<0.0001+	
HCTZ/Aml 25/10	-19.46	-5.28 (0.539)	<0.0001	
Systolic BP				
Val/HCTZ/Aml 320/25/10	-39.68			<0.0001*
Val/HCTZ 320/25	-32.04	-7.64 (0.848)	<0.0001	
Val/Aml 320/10	-33.50	-6.18 (0.846)	<0.0001+	
HCTZ/Aml 25/10	-31.48	-8.20 (0.848)	<0.0001	
Least square means and standard errors, confidence intervals, and p-values were provided by the ANCOVA model containing treatment and region as factors and centered baseline value as covariate. The Hochberg adjusted p-values are based on the maximum p-value for the three comparisons in MSDBP and the maximum p-value for the three comparisons in MSSBP. + Maximum p-values of the three comparisons.				

As can be seen from the findings above, the change from baseline in both systolic and diastolic blood pressure is significantly greater on the triple combination compared to all three double combinations.

6.1.5 Analysis of Secondary Endpoints(s)

Table 12: Overall BP control (MSSBP/MSDBP <140/90 mmHg) rate at endpoint (ITT population)

Val/HCTZ/Aml 320/25/10 Vs. Double combination	Val/HCTZ/Aml 320/25/10 n/N (%)	Double combination n/N (%)	p-value
Val/HCTZ 320/25	404/571 (70.8)	267/553 (48.3)	<0.0001 *
Val/Aml 320/10	404/571 (70.8)	302/558 (54.1)	<0.0001 *
HCTZ/Aml 25/10	404/571 (70.8)	248/554 (44.8)	<0.0001 *
P-values were from a logistic model with treatment and region as factors.			

As can be seen from the findings above, the triple combination controlled systolic and diastolic blood pressure significantly more than the three double combinations.

Figure 2: Mean ambulatory diastolic blood pressure at endpoint by hour post-dosing

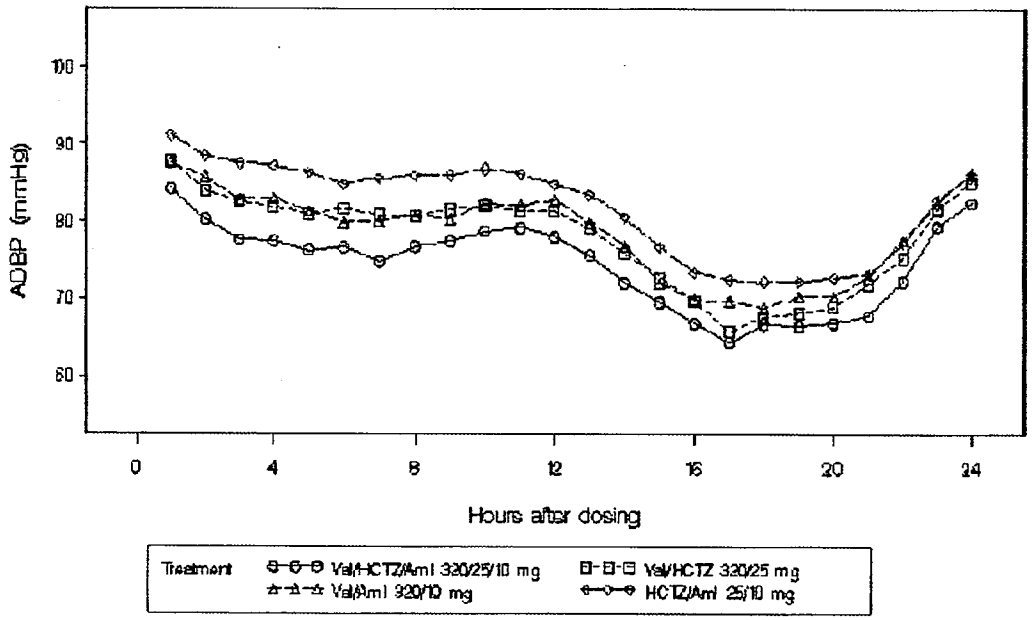
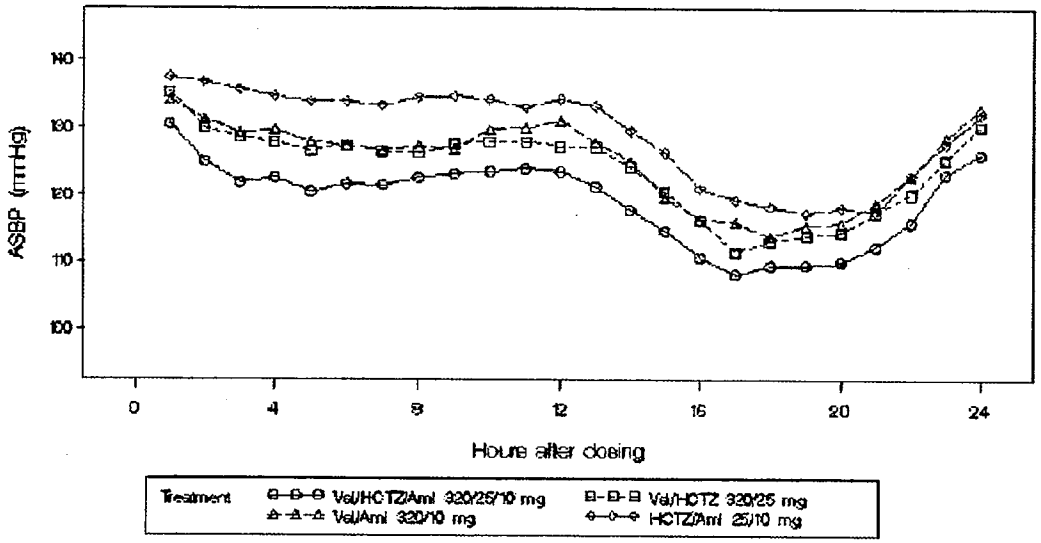


Figure 3: Mean ambulatory systolic blood pressure at endpoint by hour post-dosing



The findings in the two graphs above are based on a small sub-population sample (less than 300). These show a quick separation in ambulatory blood pressure lowering effect favoring the triple combination. This effect seems to be maintained for at least 16 hour post dosing. After 12 hours post-dosing a significant dip in blood pressure was observed on all combinations which could be explained by sleep and possibly the circadian rhythm.

Table 13: Change from baseline in diastolic and systolic ambulatory blood pressure (ABP)

	Val/HCTZ/Aml 320/25/10 mg N = 67	**Val/HCTZ 320/25 mg N = 69**	**Val/Aml 320/10 mg N = 71**	**HCTZ/Aml 25/10 mg N = 76**
Diastolic ABP				
Baseline				
Mean (SD)	94.4 (10.03)	92.8 (9.06)	93.1 (8.14)	93.4 (9.41)
Range	70.3-124.3	74.2-113.2	78.6-115.7	73.8-124.2
Endpoint				
Mean (SD)	74.5 (6.90)	77.9 (7.62)	78.7 (7.68)	81.9 (8.15)
Range	58.3-90.0	60.0-98.4	63.4-101.5	66.4-105.9
Change from baseline				
LS Mean (SE)	-19.7 (0.52)	-15.5 (0.50)	-14.9 (0.51)	-11.7 (0.47)
95% CI	(-20.72,-18.69)	(-16.46,-14.47)	(-15.87,-13.88)	(-12.59,-10.73)
p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Treatment comparisons				
Val/HCTZ/Aml vs.		Val/HCTZ	Val/Aml	HCTZ/Aml
LS Mean (SE)		-4.2 (0.70)	-4.8 (0.69)	-8.0 (0.68)
95% CI		(-5.61,-2.87)	(-6.19,-3.47)	(-9.38,-6.71)
p-value		<0.0001*	<0.0001*	<0.0001*
Systolic ABP				
Baseline				

	Val/HCTZ/Aml 320/25/10 mg N = 67	Val/HCTZ 320/25 mg N = 69	Val/Aml 320/10 mg N = 71	HCTZ/Aml 25/10 mg N = 76
Diastolic ABP				
Mean (SD)	149.6 (13.38)	146.4 (13.51)	149.7 (14.15)	147.3 (13.09)
Range	117.6-191.5	120.2-186.0	121.6-176.3	117.6-191.2
Endpoint				
Mean (SD)	119.1 (10.25)	123.8 (12.05)	125.1 (12.03)	129.1 (10.92)
Range	99.1-161.1	96.6-165.4	100.2-156.7	107.5-163.5
Change from baseline				
LS Mean (SE)	-30.3 (0.75)	-23.9 (0.73)	-24.1 (0.73)	-18.8 (0.69)
95% CI	(-31.74,-28.79)	(-25.30,-22.42)	(-25.55,-22.66)	(-20.11,-17.41)
p-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Treatment comparisons				
Val/HCTZ/Aml vs.		Val/HCTZ	Val/Aml	HCTZ/Aml
LS Mean (SE)		-6.4 (1.01)	-6.2 (1.00)	-11.5 (0.99)
95% CI		(-8.40,-4.41)	(-8.13,-4.19)	(-13.45,-9.56)
p-value		<0.0001*	<0.0001*	<0.0001*

The triple combination reduced the overall 24-hour-span blood pressures more than did all three combinations in a subpopulation of the study in which continuous blood pressure monitoring was conducted.

6.1.6 Other Endpoints

All endpoints have been covered in sections 6.1.4 and 6.1.5.

6.1.7 Subpopulations

Analyses by demographics were not pre-specified and therefore, they should be interpreted with caution.

Table 14: Between-treatment comparisons of change from baseline in mean sitting BP by gender

		LSM change from baseline	LSM difference in change (SE)	p-value
Males				
Diastolic BP				
Val/HCTZ/Aml 320/25/10	312	-24.05		
Val/HCTZ 320/25	298	-18.98	-5.07 (0.711)	<0.0001
Val/Aml 320/10	312	-20.56	-3.49 (0.703)	<0.0001
HCTZ/Aml 25/10	312	-17.92	-6.13 (0.704)	<0.0001
Systolic BP				
Val/HCTZ/Aml 320/25/10	312	-36.00		
Val/HCTZ 320/25	298	-30.28	-5.72 (1.099)	<0.0001
Val/Aml 320/10	312	-30.32	-5.68 (1.086)	<0.0001

		LSM change from baseline	LSM difference in change (SE)	p-value
HCTZ/Aml 25/10	312	-27.68	-8.32 (1.088)	<0.0001
Females				
Diastolic BP				
Val/HCTZ/Aml 320/25/10	259	-25.41		
Val/HCTZ 320/25	255	-20.41	-5.00 (0.805)	<0.0001
Val/Aml 320/10	246	-22.58	-2.82 (0.812)	0.0005
HCTZ/Aml 25/10	242	-21.39	-4.02 (0.818)	<0.0001
Systolic BP				
Val/HCTZ/Aml 320/25/10	259	-44.11		
Val/HCTZ 320/25	255	-34.23	-9.88 (1.266)	<0.0001
Val/Aml 320/10	246	-37.56	-6.55 (1.277)	<0.0001
HCTZ/Aml 25/10	242	-36.47	-7.64 (1.284)	<0.0001

No difference was observed by sex with regard to the response to the triple combination in comparison to the double combinations.

Table 15: Comparison between treatment change from baseline in mean sitting BP by race

	N	LSM change from baseline	LSM difference in change (SE)	p-value
Race: Caucasian				
Diastolic BP				
Val/HCTZ/Aml 320/25/10	417	-25.12		
Val/HCTZ 320/25	409	-19.50	-5.62 (0.622)	<0.0001
Val/Aml 320/10	399	-21.77	-3.35 (0.626)	<0.0001
HCTZ/Aml 25/10	390	-18.67	-6.44 (0.629)	<0.0001
Systolic BP				
Val/HCTZ/Aml 320/25/10	417	-40.00		
Val/HCTZ 320/25	409	-32.35	-7.65 (0.971)	<0.0001
Val/Aml 320/10	399	-34.04	-5.95 (0.977)	<0.0001
HCTZ/Aml 25/10	390	-30.63	-9.36 (0.983)	<0.0001
Race: Black				
Diastolic BP				
Val/HCTZ/Aml 320/25/10	92	-21.83		
Val/HCTZ 320/25	90	-19.32	-2.51 (1.380)	0.0700
Val/Aml 320/10	88	-18.50	-3.33 (1.381)	0.0164
HCTZ/Aml 25/10	105	-20.22	-1.61 (1.338)	0.2307
Systolic BP				
Val/HCTZ/Aml 320/25/10	92	-35.48		
Val/HCTZ 320/25	90	-29.32	-6.16 (2.306)	0.0079

Val/Aml 320/10	88	-27.20	-8.28 (2.297)	0.0004
HCTZ/Aml 25/10	105	-31.07	-4.41 (2.219)	0.0476

The number of blacks enrolled in the study is small (17%), therefore the sample size is too small to have enough power for testing the hypothesis of superiority.

As can be seen from the findings above, the difference in change between the combinations is blunted especially for diastolic BP. The triple combination does not seem to be superior to all the double combinations. Even though the number of black subjects is small, the findings are not surprising since African Americans are more responsive to diuretics than antihypertensive therapies that antagonize the rennin angiotensin system, and this could explain the blunted difference in diastolic blood pressure between the triple combination and the two combinations that contain HCTZ.

Table 16: Between-treatment comparisons of change from baseline in mean sitting BP by age

		LSM change from baseline	LSM difference in change (SE)	p-value
Age group: <65				
Diastolic BP				
Val/HCTZ/Aml 320/25/10	491	-24.40		
Val/HCTZ 320/25	477	-19.62	-4.78 (0.582)	<0.0001
Val/Aml 320/10	484	-21.08	-3.32 (0.580)	<0.0001
HCTZ/Aml 25/10	473	-18.74	-5.66 (0.584)	<0.0001
Systolic BP				
Val/HCTZ/Aml 320/25/10	491	-38.99		
Val/HCTZ 320/25	477	-31.77	-7.22 (0.906)	<0.0001
Val/Aml 320/10	484	-32.41	-6.57 (0.903)	<0.0001
HCTZ/Aml 25/10	473	-30.57	-8.42 (0.908)	<0.0001
Age group: >= 65				
Diastolic BP				
Val/HCTZ/Aml 320/25/10	80	-26.39		
Val/HCTZ 320/25	76	-20.07	-6.32 (1.318)	<0.0001
Val/Aml 320/10	74	-24.07	-2.32 (1.319)	0.0793
HCTZ/Aml 25/10	81	-23.46	-2.94 (1.287)	0.0233
Systolic BP				
Val/HCTZ/Aml 320/25/10	80	-43.91		
Val/HCTZ 320/25	76	-33.91	-10.00 (2.381)	<0.0001
Val/Aml 320/10	74	-40.52	-3.39 (2.401)	0.1589
HCTZ/Aml 25/10	81	-37.36	-6.55 (2.342)	0.0055

Only 16% of the study population was 65 years of age or older, therefore the sample size is too small to have enough power for testing the hypothesis of superiority.

Analyses by demographics performed by the sponsor were based on the model containing treatment and region as factors and centered baseline value as covariate. There was a concern

raised from the clinical review team that if other covariates, such as race, or age would have an influence on efficacy. The FDA statistical reviewer conducted an efficacy analysis by age controlling for race; and an efficacy analysis by race controlling for age. The results are similar to the sponsor's results that are not controlling for additional covariates.

6.1.7.1 Efficacy Findings by region

The analysis by study region was conducted and the result shows that the efficacy is consistent across all regions.

Table 17: Treatment comparisons for change from baseline to endpoint in sitting BP (mmHg) by region, ITT

Treatment	LSM change from baseline	LSM difference	P-value
North America - East Coast, N=512			
Diastolic BP			
Val/HCTZ/Aml 320/25/10	-21.66		
Val/HCTZ 320/25	-16.39	-5.27	<0.0001
Val/Aml 320/10	-18.68	-2.98	0.0049
HCTZ/Aml 25/10	-17.30	-4.37	<0.0001
Systolic BP			
Val/HCTZ/Aml 320/25/10	-35.53		
Val/HCTZ 320/25	-27.69	-7.83	<0.0001
Val/Aml 320/10	-30.28	-5.25	0.0032
HCTZ/Aml 25/10	-29.13	-6.39	0.0003
Europe, N=607			
Diastolic BP			
Val/HCTZ/Aml 320/25/10	-25.40		
Val/HCTZ 320/25	-20.61	-4.78	<0.0001
Val/Aml 320/10	-22.22	-3.18	0.0025
HCTZ/Aml 25/10	-19.99	-5.41	<0.0001
Systolic BP			
Val/HCTZ/Aml 320/25/10	-42.80		
Val/HCTZ 320/25	-35.96	-6.84	<0.0001
Val/Aml 320/10	-36.09	-6.71	<0.0001
HCTZ/Aml 25/10	-34.12	-8.67	<0.0001
South America, N=477			
Diastolic BP			
Val/HCTZ/Aml 320/25/10	-28.90		

Val/HCTZ 320/25	-22.24	-6.66	<0.0001
Val/Aml 320/10	24.33	-4.57	<0.0001
HCTZ/Aml 25/10	-23.46	-5.44	<0.0001
Systolic BP			
Val/HCTZ/Aml 320/25/10	-45.22		
Val/HCTZ 320/25	-33.37	-11.86	<0.0001
Val/Aml 320/10	-37.03	-8.19	<0.0001
HCTZ/Aml 25/10	-35.86	-9.37	<0.0001
North America-West, N=640			
Diastolic BP			
Val/HCTZ/Aml 320/25/10	-23.12		
Val/HCTZ 320/25	-19.28	-3.84	0.0004
Val/Aml 320/10	-20.41	-2.71	0.0116
HCTZ/Aml 25/10	-17.49	-5.63	<0.0001
Systolic BP			
Val/HCTZ/Aml 320/25/10	-35.63		
Val/HCTZ 320/25	-30.59	-5.04	0.0019
Val/Aml 320/10	-30.68	-4.95	0.0021
HCTZ/Aml 25/10	-27.37	-8.26	<0.0001

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dosing recommendations for Exforge HCT were based on highest usual doses of the individual components (detailed in prior NDAs). No further explorations were done.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Studies of persistence of efficacy and/or tolerance effects were not done for this triple combination

6.1.10 Additional Efficacy Issues/Analyses: Statistical Comments

In reviewing the study protocol, the FDA statistical reviewer commented that Hochberg's procedure controls the error rate only under certain strict conditions that are difficult to verify and recommended Holm's procedure be used. However, Hochberg's procedure was still used in the sponsor's analysis. Verifying the results by using both procedures, the conclusion of efficacy is the same since the p- values are somewhat small.

7 Review of Safety

Summary of Safety

Primary interpretation of the safety data for Exforge HCT, a combination of valsartan, hydrochlorothiazide, and amlodipine at maximal/highest usual doses (320/25/10), is based on the confirmatory study, VEA A2302, a double-blind, randomized, active-controlled, parallel-group trial designed to evaluate the triple combination compared with the 3 dual combinations (valsartan/HCTZ 320/25, valsartan/amlodipine 320/10, and HCTZ/amlodipine 25/10). In the confirmatory study, there were 582 subjects in the triple therapy arm safety population and 2268 subjects in the total safety population (subjects from all four of the arms combined). The subjects were, as a group, young, with a mean age of 53.3 ± 10 yrs, which is a notably younger mean age than that of patients with hypertension outside of clinical trial arena, and only 14% of the subjects were 65 years of age or older.

There were no deaths in the confirmatory study, or in any of the 10 studies of Exforge HCT. There were 21 subjects in the confirmatory study who experienced non-fatal serious adverse events, 5 of these in the triple therapy arm, 7 in the valsartan/HCTZ arm, 4 in the valsartan/amlodipine arm, and 5 in the HCTZ/amlodipine arm. With regard to discontinuations, upon analysis of the Case Report Forms, there were 83 subjects in whom the study drug was permanently discontinued in the confirmatory study. Notable among these were 24 cases of discontinuation due to dizziness and hypotension, of which 9 were in the triple therapy group, 11 in the valsartan/hydrochlorothiazide group, 3 in the valsartan/amlodipine group, and 1 in the HCTZ/amlodipine group. There were 2 discontinuations due to pregnancy in the study, both in the triple therapy group, one of which resulted in the delivery of a healthy newborn and the second of which was terminated.

The most frequently observed adverse events in the triple therapy subjects of the pivotal study were dizziness and edema. Of these two, dizziness was found at a greater frequency in the triple therapy subjects than in any of the three other dual therapy subjects. **According to the sponsor's** MedDRA coding, dizziness was found at 7.7% in the triple therapy group, 7.0% in the valsartan/HCTZ group, 3.9% in the HCTZ/amlodipine group, and 2.3% in the valsartan/amlodipine group. Hypotension was 1.4% in the triple therapy group, 1.3% in the valsartan/HCTZ group, 0% in the HCTZ/amlodipine group, and 0.4% in the valsartan/amlodipine group. However, if the terms dizziness, dizziness exertional, and dizziness postural are pooled together, the frequency of the pooled event of dizziness is 9.1% in the triple therapy group, 8.2% in the valsartan/HCTZ group, 4.3% in the HCTZ/amlodipine group, and 2.7% in the valsartan/amlodipine group. Similarly, with edema, the sponsor used the term peripheral edema alone. If, however, one pools the terms edema, generalized edema, gravitational edema, peripheral edema, and pitting edema, the percentage of subjects with the pooled term of edema is much higher. The frequency of edema, both using the stand-alone term of peripheral edema as done by the sponsor or pooling of several of the peripheral edema terms as done by the reviewer, results in edema frequencies in the triple therapy subjects being lower than that seen in both the HCTZ/amlodipine and valsartan/amlodipine groups but higher than the

percentage seen in the valsartan/HCTZ group. In the first case, with peripheral edema as a stand alone term, the percentages were 4.5% in the triple therapy group, 8.9% and 8.5% in the HCTZ/amlodipine and valsartan/amlodipine groups respectively, and 0.9% in the valsartan/HCTZ group. In the second case, with the pooled edema term, the percentages were increased to 7.0% in the triple therapy group, 11.9% and 13.4% in the HCTZ/amlodipine and valsartan/amlodipine groups respectively, and 1.4% in the valsartan/HCTZ group. Thus, the frequency of dizziness/hypotension was highest with the triple therapy regimen as opposed to all of the dual therapy regimens but the frequency of edema with the triple therapy regimen was less than the two amlodipine-containing regimens (HCTZ/amlodipine and valsartan/amlodipine) but higher than that seen with the non-amlodipine-containing dual therapy regimen (valsartan/HCTZ). The data were not sufficient, however, to characterize these adverse events with regard to time course, either from the time of onset of initiation of therapy or with regard to the time of intake of individual doses. Also, considering that the study subjects were in general younger than the population likely to be treated with this combination anti-hypertensive, one might expect elderly patients to be more sensitive to the dizziness/hypotension. This was suggested by the subgroup analysis of adverse events, as the pooled term hypotension was seen at a greater percentage in the subjects 65 years of age or older, but this analysis was limited by the low number of subjects in the older subgroup.

Thus, there did not appear to be any strong safety signals with the triple therapy regimen in the population studied. Furthermore, given that Exforge HCT is not a novel entity, and all of its individual components have been used for a significant time, both alone and in combination, the side effects of these therapies are fairly well known to health care practitioners. In conclusion, this reviewer finds the safety profile for Exforge HCT to be acceptable.

The draft of the label provided by the sponsors does need to be amended to include the incidence of dizziness and edema that are pooled according to clinical relevance, rather than relying on the narrow breadown of the preferred terms as has been done.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

7.1.1.1 Clinical Studies Used to Evaluate Safety

Ten studies, of which 9 are complete and 1 is an ongoing study, have been included in the sponsor's safety review of Exforge HCT, a combination of valsartan, hydrochlorothiazide, and amlodipine at maximal/highest usual doses (320/25/10). Primary interpretation of the safety data for the triple combination by the sponsor is based on the confirmatory study, VEA A2302, and a supportive open-label study, VEA ABR01, both of which were conducted for efficacy and safety and the only studies which involved randomization of subjects to triple therapy. The safety data from all of the studies were not pooled given the differing study designs and the absence of an adequate control group (in all of the studies with the exception of study VEA A2302, which did have a control group). Within each study, the safety population consisted of subjects who

received at least one dose of study drug. In this safety review, the primary focus will be on the confirmatory study, VEA A2302, referred to by the sponsor as the pivotal study.

The safety population of the confirmatory study, VEA A2302, which is a large, phase III, randomized, active-control, double-blind trial of triple therapy versus each of the dual combinations (valsartan/amlodipine, valsartan/HCTZ, and HCTZ/amlodipine) consists of 2268 subjects, with 559 to 582 subjects per treatment arm and 582 subjects on triple therapy.

The safety population of the supportive study, VEA ABR01, includes 340 subjects, with 264 of these subjects receiving triple therapy. The remainder of the studies consisted of uncontrolled trial designs in which the triple therapy was given as an optional, open-label addition of either HCTZ to valsartan/amlodipine (the VAA studies), or the VAH studies, which consisted of those studies in which amlodipine was added to valsartan/HCTZ, or valsartan was added to HCTZ/amlodipine towards the late phase of the study. Across these uncontrolled studies, the number of subjects in the safety population who received triple combination therapy were 196 in study VAA A2401, 147 in study VAA A2402, 136 in study VAA A2403, 72 in study VAH BUS04, 66 in study VAH BDE13E1, and 79 in study VAH B2496E1. Finally, in the long-term study, VAA A2201E1, which involved the optional addition of hydrochlorothiazide to valsartan/amlodipine, given that some subjects might be counted in more than one treatment group, it is unclear exactly how many subjects ultimately received triple therapy, though this number falls somewhere within the range of 247 and 271.

7.1.1.2 Rationale for Choice of Studies Included in this Safety Review

After review of all of the studies, there was nothing that appeared to stand out from the uncontrolled studies in this series. Given that all of these studies had no controls, were small studies, could not be pooled due to differing study designs, had open-label, often optional, additions of treatment, and were non-randomized (with the exception of ABR01 which was randomized but uncontrolled), we did not focus on these in this review. Instead, the primary focus of this review will be on the confirmatory study, VEA A2302.

7.1.1.3 Study Methodology, including Dosing Overview and Duration of Treatment

The confirmatory study is a multi-center, double-blind, randomized, active-controlled, parallel-group trial conducted in 15 countries including the US, designed to evaluate the triple combination compared with the 3 dual combinations. Subjects had their existing anti-hypertensive therapy withdrawn (or slowly tapered if necessary) and entered the 1 week single-blind placebo run-in period, after which they then returned for a follow-up visit to determine eligibility based on blood pressure. Subjects with MSDBP $\geq$ 100 and < 120 mmHg, and MSSBP $\geq$ 145 and < 200 mmHg were randomized at this time. Subjects who did not meet these blood pressure criteria were randomized after 2-3 weeks if they met the criteria. Randomization was done in a double-blind manner to **one of four treatment groups – valsartan/HCTZ/amlodipine** 160/12.5/0 mg qd, valsartan/HCTZ 160/12.5 mg qd, valsartan/amlodipine 160/5 mg qd, and HCTZ/amlodipine 12.5/5 mg qd. They were then force-titrated over a two-week period to the

maximum doses of valsartan/HCTZ/amlodipine 320/25/10 mg qd, valsartan/HCTZ 320/25 mg qd, valsartan/amlodipine 320/10 mg qd, and HCTZ/amlodipine 25/10 mg qd. Treatment at these maximal doses was continued for 6 weeks until study completion, with no downward dose adjustment permitted. Thus, the maximal duration of a subject's participation in the trial was 13 weeks (5 weeks maximum single-blind washout if prior antihypertensive therapy required slow taper and 8 weeks of double-blind treatment).

7.1.2 Categorization of Adverse Events

The coding of the sponsor was assessed through the comparison of the verbatim terms of adverse events with the MedDRA preferred terms along with review of the submitted Case Report Forms. Overall, the coding was deemed adequate. We did find, however, a systematic issue with coding a similar medical concept into different preferred terms. This was of particular relevance with adverse events such as edema. The sponsor coded the occurrences of edema as generalized oedema, gravitational oedema, oedema, peripheral oedema, and pitting oedema. As a result of this narrow coding, if one looked at the rates of edema, the incidence of simply the preferred term 'oedema' alone would be lower than the true incidence of the occurrence of the adverse event edema. This was also true of dizziness, hypotension, polyuria, etc. Thus, we assessed the adverse event data not only as coded by the sponsor but as pooled into categories of adverse events as deemed clinically relevant by us.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The safety data from all of the studies were not pooled given the differing study designs and the absence of an adequate control group in all of the studies except for VEA A2302, the confirmatory study, which did have a control group.

7.2 Adequacy of Safety Assessments

The total number of subjects exposed to triple therapy in the safety population across this series of studies was between 1789 and 1813. This safety population includes one phase III, randomized, controlled double-blind study (the confirmatory study), a second supportive study, and a third long term safety study, along with numerous smaller, uncontrolled studies with partial open-label or open-label extension study designs. This series of studies is adequate for premarket evaluation of safety.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Extent of Exposure

In the confirmatory study, exposure was similar across the treatment groups, with the majority of subjects exposed for 50 days or more, consistent with the 8 week duration of treatment in the study, as shown in Table 18.

Table 18: Sponsor's table of Duration of exposure to study drug by treatment group in the confirmatory study

Duration of exposure (days)	Val/HCTZ/Aml 320/25/10 mg N=582	Val/HCTZ 320/25 mg N=559	Val/Aml 320/10 mg N=566	HCTZ/Aml 25/10 mg N=561	Total N=2268
Mean (SD)	53.7 (12.16)	53.9 (12.52)	55.0 (10.59)	54.1 (11.83)	54.1 (11.80)
Median	56.0	56.0	56.0	56.0	56.0
Range	1-87	1-161	1-104	1-92	1-161
Overall days of exposure by interval (n %)					
1 - 7 days	14 (2.4)	7 (1.3)	8 (1.4)	10 (1.8)	39 (1.7)
8 - 14 days	7 (1.2)	10 (1.8)	6 (1.1)	10 (1.8)	33 (1.5)
15 – 28 days	15 (2.6)	20 (3.6)	8 (1.4)	12 (2.1)	55 (2.4)
29 - 42 days	16 (2.7)	20 (3.6)	13 (2.3)	17 (3.0)	66 (2.9)
43 - 49 days	16 (2.7)	7 (1.3)	11 (1.9)	6 (1.1)	40 (1.8)
50 - 56 days	288 (49.5)	260 (46.5)	291 (51.4)	269 (48.0)	1108 (48.9)
57+ days	226 (38.8)	235 (42.0)	229 (40.5)	237 (42.2)	927 (40.9)

[Source: Table 1-7, Summary of Clinical Safety, Novartis Pharmaceuticals]

7.2.1.2 Demographics

Demographic characteristics of the subjects from the confirmatory study are shown in Table 19. Overall, the study population was of a younger age than that of the hypertensive population at large, which is often the case with clinical trials in hypertension. This would have tendency to downplay the adverse events that might be seen in an older population with a greater number of baseline medical problems and differing sensitivities to adverse events.

Table 19: Sponsor's table of demographics by treatment in the confirmatory study

Demographic variable	Val/HCTZ/Aml 320/25/10 mg N=583	Val/HCTZ 320/25 mg N=559	Val/Aml 320/10 mg N=568	HCTZ/Aml 25/10 mg N=561	Total N=2271
Sex					
Male	316 (54.2%)	303 (54.2%)	319 (56.2%)	317 (56.5%)	1255 (55.3%)
Female	267 (45.8%)	256 (45.8%)	249 (43.8%)	244 (43.5%)	1016 (44.7%)
Age group (<65; ≥ 65)					
<65	501 (85.9%)	483 (86.4%)	492 (86.6%)	478 (85.2%)	1954 (86.0%)
≥ 65	82 (14.1%)	76 (13.6%)	76 (13.4%)	83 (14.8%)	317 (14.0%)
Age group (<75; ≥ 75)					
<75	570 (97.8%)	552 (98.7%)	554 (97.5%)	553 (98.6%)	2229 (98.2%)
≥ 75	13 (2.2%)	7 (1.3%)	14 (2.5%)	8 (1.4%)	42 (1.8%)
Age (years)					
n	583	559	568	561	2271
Mean (SD)	53.3 (10.28)	53.1 (10.36)	52.8 (10.29)	53.6 (10.13)	53.2 (10.26)
Range	20-82	21-84	23-83	19-82	19-84
Race					
Caucasian	420 (72.0%)	412 (73.7%)	403 (71.0%)	392 (69.9%)	1627 (71.6%)
Black	98 (16.8%)	93 (16.6%)	91 (16.0%)	107 (19.1%)	389 (17.1%)
Asian	4 (0.7%)	6 (1.1%)	10 (1.8%)	7 (1.2%)	27 (1.2%)
Native American	3 (0.5%)	3 (0.5%)	8 (1.4%)	4 (0.7%)	18 (0.8%)
Pacific Islander	2 (0.3%)	2 (0.4%)	1 (0.2%)	0 (0.0%)	5 (0.2%)
Other	56 (9.6%)	43 (7.7%)	55 (9.7%)	51 (9.1%)	205 (9.0%)
Body Mass Index (kg/m^2)					
n	581	554	565	557	2257
Mean (SD)	32.2 (6.91)	32.3 (6.95)	31.8 (6.41)	31.5 (6.07)	32.0 (6.60)
Range	20-78	18-83	19-60	16-57	16-83

Note: All the demographic variables are taken from Visit 1, except weight. Weight was measured at Visit 3 (Week 1). If Visit 3 weight value was not available, Visit 1 (screening) value was used. BMI is calculated.
Source: [Study VEA A2302-PTT 14.1-3.1]

[Source: Table 1-17, Summary of Clinical Safety, Novartis Pharmaceuticals]

7.2.1.3 Baseline Disease Characteristics: Blood Pressure

In the confirmatory study, the baseline mean sitting systolic/diastolic blood pressure (MSSBP/MSDBP) was 169.9/106.5 mmHg in the total population and values were comparable across the 4 treatment groups (169.6/106.4 in the triple therapy arm). Standing systolic/diastolic blood pressure (BP) was also consistent across groups, with a mean of 169.1/108.5 for the total population and 169.1/108.5 for the triple therapy subjects.

7.2.2 Explorations for Dose Response

Given that Exforge HCT is a combination product of already used doses of valsartan, hydrochlorothiazide, and amlodipine, dose response studies were not performed. Instead, maximal/highest usual doses were used for the confirmatory study, both in the dual therapy regimens and in the triple combination therapy being assessed for this NDA.

7.2.3 Special Animal and/or In Vitro Testing

For this triple combination product of approved drug components, special animal testing and/or *in vitro* testing was not indicated.

7.2.4 Routine Clinical Testing

Routine clinical testing was adequate in the study, with monitoring of vital signs including blood pressure and appropriate laboratory data.

7.2.5 Metabolic, Clearance, and Interaction Workup

Workup for interaction effects was carried out. The drug interaction study (study number VEA489A2104) showed no clinically significant pharmacokinetic drug interaction between the components (Valsartan, Hydrochlorothiazide, and Amlodipine) of Exforge HCT.

Please see the Clinical Pharmacology Review by Dr. Menon-Andersen for complete details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The primary adverse events of relevance for similar drugs in the drug class of Exforge HCT are dizziness, hypotension, and edema, all of which have been covered in depth in this safety review.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in these studies.

7.3.2 Nonfatal Serious Adverse Events

Twenty-one subjects in the confirmatory study (0.9%) experienced serious adverse events [SAEs] which occurred during the double-blind period. Five of these were in the triple therapy group, 7 in the val/HCTZ group, 4 in the val/aml group, and 5 subjects in the HCTZ/aml group. Of the submitted case report forms analyzed by the reviewer, there were 18 SAEs for which the investigational therapy was discontinued (1 of these was during the single blind run-in and the rest were during the double-blind period). These SAE discontinuations included 1 case of acute renal failure, 1 cardiac and 1 non-cardiac chest pain, 1 'retrosternal chest pain' (unclear as to whether cardiac or non-cardiac), 3 cerebrovascular accidents, 1 case of congestive heart failure, 2 cases of dizziness and hypotension, 1 case of alcoholic pancreatitis, 1 case of bilateral hydronephrosis, 3 cases of myocardial infarction, 2 cases of worsening hypertension/hypertensive crisis, and 1 case of vaginal bleeding.

7.3.3 Dropouts and/or Discontinuations

In the confirmatory study, 2271 subjects were randomized, and, of these, 2060 subjects (90.7% of those randomized) completed **the study per the sponsor's analysis.** These rates were similar across treatment groups, as can be seen in Table 20.

Table 20: Participation and Withdrawals in the confirmatory study

Treatment	**V/H/A 320/25/10 n (%)**	**V/H 320/25 n (%)**	**V/A 320/10 n (%)**	**H/A 25/10 n (%)**	**Total n (%)**
Total N	583	559	568	561	2271
Completed	522 (89.5)	506 (90.5)	526 (92.6)	506 (90.2)	2060 (90.7)
Discontinued	61 (10.5)	53 (9.5)	42 (7.4)	55 (9.8)	211 (9.3)
AE	24 (4.1)	17 (3.0)	10 (1.8)	20 (3.6)	71 (3.1)
Withdrew consent	11 (1.9)	13 (2.3)	15 (2.6)	17 (3.0)	56 (2.5)
Loss to follow-up	8 (1.4)	11 (2.0)	10 (1.8)	6 (1.1)	35 (1.5)
Therapy unsatisfactory	4 (0.7)	6 (1.1)	0 (0.0)	7 (1.2)	17 (0.7)
Admin problems	5 (0.9)	2 (0.4)	5 (0.9)	3 (0.5)	15 (0.7)
Protocol Violation	9 (1.5)	1 (0.2)	2 (0.4)	2 (0.4)	14 (0.6)
Therapy no longer required	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.1)
Abnormal labs	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.0)

[Source: Adapted from Table 1-26, Summary of Clinical Safety, Novartis Pharmaceuticals]

We analyzed the submitted Case Report Forms (CRFs) of the confirmatory study, and found that there were 83 subjects in whom the study drug was permanently discontinued in the pivotal study. The majority (27) of these were in the triple therapy group, as can be seen in Table 21. Hypotension and dizziness were the most common cause for discontinuation (24 subjects in total), followed by edema (10 subjects), headache (6 subjects), and flushing (3 subjects). There were 2 discontinuations due to pregnancies, both of which were in the triple therapy group. Of note, there were 2 discontinuations due to possible allergic reactions to the study drug, and 3 discontinuations related to renal dysfunction. Of the 24 cases of dizziness and hypotension

resulting in discontinuation, 2 were characterized as serious adverse events (SAE), while none of the 11 cases of edema contributing to discontinuation were marked as SAEs. There were 18 **subjects who had discontinuations due to serious adverse events in the submitted CRF's. These** SAE discontinuations included 1 case of acute renal failure, 1 cardiac and 1 non-cardiac chest **pain, 1 'retrosternal chest pain' (unclear whether cardiac or non-cardiac)**, 3 cerebrovascular accidents, 1 case of congestive heart failure, 2 cases of dizziness and hypotension, 1 case of alcoholic pancreatitis, 1 case of bilateral hydronephrosis, 3 cases of myocardial infarction, 2 cases of worsening hypertension/hypertensive crisis, and 1 case of vaginal bleeding.

Table 21: Reviewer's table of permanent discontinuations due to adverse events/protocol violations/laboratory abnormalities in the confirmatory study, per reviewer's analysis of submitted Case Report Forms

Adverse Events	*Total n* N=83	*H/A 25/10* N=25	*V/A 320/10* N=11	*V/H 320/25* N=20	*V/H/A 320/25/10* N=27
Dizziness/hypotension	24	1	3	11	9
Edema	10	5	4	0	1
Headache	6	4	0	1	1
Flushing	3	2	1	0	0
Allergic reaction	2	1	1	0	0
CVA	2	1	0	0	1
Elevated BP	2	1	0	1	0
Fatigue & lethargy	2	1	0	1	0
Hypokalemia	2	1	0	0	1
Myocardial infarction	2	1	0	0	1
Nausea/vomiting	2	1	0	1	0
Pregnancy	2	0	0	0	2
Rash	2	0	1	1	0
Abdominal pain	1	0	0	0	1
ARF	1	0	0	0	1
Atrial fibrillation	1	0	1	0	0
Breast lump	1	1	0	0	0
Cardiac chest pain	1	1	0	0	0
Cold symptoms	1	0	0	0	1
Worsening Depression	1	0	0	0	1
Elevated BUN	1	0	0	0	1
Elevated creatinine	1	0	0	1	0
EtOH pancreatitis	1	0	0	0	1

Adverse Events	*Total n* N=83	*H/A 25/10* N=25	*V/A 320/10* N=11	*V/H 320/25* N=20	*V/H/A 320/25/10* N=27
Frequent urination	1	0	0	0	1
Hyponatremia	1	1	0	0	0
Lack of attention	1	0	0	0	1
Left arm numbness	1	0	0	1	0
Leukopenia	1	0	0	0	1
Myalgia	1	1	0	0	0
Nervousness	1	1	0	0	0
Non-cardiac chest pain	1	1	0	0	0
Renal insufficiency	1	0	0	1	0
Retrosternal pain	1	0	0	1	0
Stomach gripes	1	0	0	0	1
Tachycardia	1	0	0	0	1

[Source: FDA Clinical Reviewer's Analysis]

7.3.4 Significant Adverse Events

In the confirmatory study, there were relatively similar numbers of adverse events by severity class in each treatment group, as can be seen in Table 22. In Table 23, the most frequent severe adverse events in the confirmatory study are listed, in descending order of frequency, by treatment category.

Table 22: Reviewer's table of adverse events by severity class and treatment, in the confirmatory study, in those subjects who received randomized therapy

AE Severity	Total	H/A 25/10	V/A 320/10	V/H 320/25	V/H/A 320/25/10
1	1347	349	341	313	344
2	624	132	147	167	178
3	86	14	23	28	21

[Source: FDA Clinical Reviewer's Analysis]

Table 23: Reviewer's table of most frequently observed severe AE (Severity Score of 3) in the confirmatory study, by sponsor's coding of preferred terms and by treatment, in those subjects who received randomized therapy

AE Preferred Term	Total	H/A 25/10	V/A 320/10	V/H 320/25	V/H/A 320/25/10
Headache	6	2	1	2	1
Dizziness	5	0	1	2	2
Hypotension	4	0	0	2	2
Abdominal Pain Upper	3	0	0	3	0
Back Pain	3	3	0	0	0
Abdominal Pain	2	0	0	1	1
Arthralgia	2	0	1	1	0
Diarrhoea	2	0	1	1	0
Fall	2	0	0	0	2
Fatigue	2	0	2	0	0
Haemorrhoids	2	1	0	1	0
Lethargy	2	0	1	1	0
Muscle Spasms	2	1	0	0	1
Nausea	2	0	0	0	2
Oedema peripheral	2	0	2	0	0

(Note: The AE in this table may be present more than once in an individual subject, as they are displayed by occurrence, not by subject.)

[Source: FDA Clinical Reviewer's Analysis]

7.3.5 Submission Specific Primary Safety Concerns

The major safety concerns specific to this product are those of hypotension and edema, both of which are covered in depth in this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the confirmatory study, VEA A2302, the most frequently observed adverse events (AEs) in the total safety population as per **the sponsor's analysis, were dizz**iness (5.2%), peripheral edema (5.7%) and headache (5.4%). Dizziness occurred with greater frequency in the triple therapy (7.7%) and valsartan/HCTZ (7.0%) arms than in the valsartan/amlodipine (2.3%) or HCTZ/amlodipine (3.9%) arms. Peripheral edema occurred with greater frequency in the

HCTZ/amlodipine (8.9%) and valsartan/amlodipine (8.5%) arms than in the triple therapy (4.5%) or valsartan/HCTZ (0.9%) arms. Otherwise, the frequencies were similar across the treatment arms. The sponsors then pooled edema and peripheral edema, and found that the incidence was significantly less in the triple therapy arm (4.5%) than in the 2 amlodipine-containing dual regimen groups (8.5% and 8.9% in the val/aml 320/10 and HCTZ/Aml 25/10 arms, respectively) but greater than that seen in the valsartan/HCTZ group (0.9%). This was significant for all comparisons (p=0.0029, 0.0057, and 0.0002 for triple therapy versus HCTZ/aml, val/aml, and val/HCTZ, respectively). They also found that hypotension, syncope, and orthostatic hypotension were found at greater frequency in the triple therapy and valsartan/HCTZ groups that in the remaining two dual therapy groups. Table 24 shows adverse events by treatment category (greater than or equal to 2% in any triple therapy group) by MeDRA preferred term and treatment, in the confirmatory study.

Table 24: Sponsor's table of adverse events by treatment (≥ 2% in any triple therapy group) in the confirmatory study, regardless of relationship to treatment, by MedDRA preferred term and treatment

	V/H/A 320/25/10 N=582	**V/H 320/25** N=559	**V/A 320/10** N=566	**H/A 25/10** N=561	**Total** N=2268
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Any preferred term	263 (45.2)	253 (45.3)	254 (44.9)	271 (48.3)	1041 (45.9)
Dizziness	45 (7.7)	39 (7.0)	13 (2.3)	22 (3.9)	119 (5.2)
Oedema peripheral	26 (4.5)	5 (0.9)	48 (8.5)	50 (8.9)	129 (5.7)
Headache	25 (4.3)	30 (5.4)	28 (4.9)	39 (7.0)	122 (5.4)
Dyspepsia	13 (2.2)	5 (0.9)	6 (1.1)	2 (0.4)	26 (1.1)
Fatigue	13 (2.2)	15 (2.7)	12 (2.1)	8 (1.4)	48 (2.1)
Muscle spasms	13 (2.2)	7 (1.3)	7 (1.2)	5 (0.9)	32 (1.4)
Back pain	12 (2.1)	13 (2.3)	5 (0.9)	12 (2.1)	42 (1.9)
Nasopharyngitis	12 (2.1)	13 (2.3)	13 (2.3)	12 (2.1)	50 (2.2)
Nausea	12 (2.1)	7 (1.3)	10 (1.8)	12 (2.1)	41 (1.8)

[Source: Adapted from Table 2-1, Summary of Clinical Safety, Novartis Pharmaceuticals]

We repeated the analysis of adverse events in the confirmatory study initially as coded by the sponsor, and then as pooled into groups of related adverse event by the reviewer. This can be seen in Table 25 (analysis performed by the reviewer **using the sponsor's coding of preferred** terms), and Table 26 (pooled by the reviewer according to subgroups of related adverse events). When the data were analyzed as coded by the sponsor, without pooling, the adverse events seen at the greatest frequency in the triple therapy subjects, were, in descending order, dizziness, oedema peripheral, headache, dyspepsia, and fatigue. With pooling into groups of related adverse events, the most frequent pooled adverse events in the triple therapy subjects were (once

again in descending order) the pooled terms of dizziness, edema, headache, dyspepsia, and fatigue and lethargy, similar to the unpooled order, but with increased percentages in each category as per the pooling. After pooling the number of triple therapy subjects in the pivotal study with MeDRA preferred term pooled to dizziness was 53, or 9.1%, and the number pooled into the edema category was 41, or 7.0%. As can be seen in Table 26, the frequency of the pooled term dizziness was greater in the triple therapy subjects than in any of the dual therapy arms, while that of edema was greater in the triple therapy arm (7.0%) than in the non-amlodipine-containing group (1.4%) but less than that seen in the two amlodipine-containing dual therapy groups (11.9% and 13.4% in the hydrochlorothiazide/amlodipine and valsartan/amlodipine groups, respectively).

Table 25: Reviewer's table of the 20 Most Frequent AE (as coded by sponsor – MEDRA Preferred Terms) in the confirmatory study (in descending order of AE in triple therapy subjects)

AE (Preferred Term)	**V/H/A 320/25/10**	**H/A 25/10**	**V/A 320/10**	**V/H 320/25**	**Total**
	N = 582	*N = 561*	*N = 566*	*N = 559*	*N = 2268*
Dizziness	45 (7.7)	22 (3.9)	13 (2.3)	39 (7.0)	119 (5.2)
Edema peripheral	26 (4.5)	50 (8.9)	48 (8.5)	5 (0.9)	129 (5.7)
Headache	25 (4.3)	39 (7.0)	28 (4.9)	30 (5.4)	122 (5.4)
Dyspepsia	13 (2.2)	2 (0.4)	6 (1.1)	5 (0.9)	26 (1.1)
Fatigue	13 (2.2)	8 (1.4)	12 (2.1)	15 (2.7)	48 (2.1)
Muscle spasms	13 (2.2)	5 (0.9)	7 (1.2)	7 (1.3)	32 (1.4)
Back pain	12 (2.1)	12 (2.1)	5 (0.9)	13 (2.3)	42 (1.9)
Nasopharyngitis	12 (2.1)	12 (2.1)	13 (2.3)	13 (2.3)	50 (2.2)
Nausea	12 (2.1)	12 (2.1)	10 (1.8)	7 (1.3)	41 (1.8)
Asthenia	11 (1.9)	2 (0.4)	3 (0.5)	3 (0.5)	19 (0.8)
URI	10 (1.7)	6 (1.1)	8 (1.4)	11 (2.0)	35 (1.5)
Diarrhea	9 (1.5)	7 (1.2)	15 (2.7)	10 (1.8)	41 (1.8)
Abdominal pain upper	8 (1.4)	0 (0.0)	8 (1.4)	5 (0.9)	21 (0.9)
Hypotension	8 (1.4)	0 (0.0)	2 (0.4)	7 (1.3)	17 (0.7)
Pollakiuria	8 (1.4)	0 (0.0)	1 (0.2)	1 (0.2)	10 (0.4)
Bronchitis	7 (1.2)	3 (0.5)	0 (0.0)	4 (0.7)	14 (0.6)
Edema	7 (1.2)	11 (2.0)	15 (2.7)	3 (0.5)	36 (1.6)
Dyspnea	6 (1.0)	2 (0.4)	1 (0.2)	4 (0.7)	13 (0.6)
Hypokalemia	6 (1.0)	6 (1.1)	1 (0.2)	1 (0.2)	14 (0.6)
Nasal congestion	5 (0.9)	4 (0.7)	5 (0.9)	1 (0.2)	15 (0.7)

[Source: FDA Clinical Reviewer's Analysis]

Table 26: Reviewer's table of the 20 Most Frequent AE (pooled by the reviewer) in the confirmatory study (in descending order of AE in triple therapy subjects)

Pooled AE	V/H/A 320/25/10	H/A 25/10	V/A 320/10	V/H 320/25	Total
	N = 582	*N = 561*	*N = 566*	*N = 559*	*N = 2268*
Dizziness	53 (9.1)	24 (4.3)	15 (2.7)	46 (8.2)	138 (6.1)
Edema	41 (7.0)	67 (11.9)	76 (13.4)	8 (1.4)	192 (8.5)
Headache	33 (5.7)	50 (8.9)	34 (6.0)	37 (6.6)	154 (6.8)
Dyspepsia	19 (3.3)	3 (0.5)	6 (1.1)	6 (1.1)	34 (1.5)
Fatigue & lethargy	17 (2.9)	11 (2.0)	14 (2.5)	19 (3.4)	61 (2.7)
Nausea & vomiting	16 (2.7)	15 (2.7)	16 (2.8)	10 (1.8)	57 (2.5)
Abdominal discomfort	14 (2.4)	8 (1.4)	12 (2.1)	15 (2.7)	49 (2.2)
Back pain	14 (2.4)	15 (2.7)	5 (0.9)	15 (2.7)	49 (2.2)
Muscle spasms	13 (2.2)	5 (0.9)	8 (1.4)	10 (1.8)	36 (1.6)
Asthenia	12 (2.1)	2 (0.4)	3 (0.5)	3 (0.5)	20 (0.9)
Nasopharyngitis	12 (2.1)	12 (2.1)	13 (2.3)	12 (2.1)	49 (2.2)
Hypotension	11 (1.9)	1 (0.2)	2 (0.4)	8 (1.4)	22 (1.0)
Upper respiratory infection	10 (1.7)	6 (1.1)	8 (1.4)	12 (2.1)	36 (1.6)
Diarrhea	9 (1.5)	7 (1.2)	19 (3.4)	12 (2.1)	47 (2.1)
Polyuria	9 (1.5)	3 (0.5)	2 (0.4)	2 (0.4)	16 (0.7)
Bronchitis	8 (1.4)	3 (0.5)	0 (0.0)	4 (0.7)	15 (0.7)
Hypokalemia	7 (1.2)	12 (2.1)	3 (0.5)	2 (0.4)	24 (1.1)
Dyspnea	6 (1.0)	2 (0.4)	1 (0.2)	4 (0.7)	13 (0.6)
Hyperglycemia/DM	5 (0.9)	2 (0.4)	8 (1.4)	0 (0.0)	15 (0.7)
Erectile Dysfunction	5 (0.9)	2 (0.4)	1 (0.2)	4 (0.7)	12 (0.5)

Note - Pooling of AE is as follows: dizziness (dizziness, dizziness exertional, dizziness postural); edema (generalized oedema, gravitational oedema, oedema, peripheral oedema, pitting oedema); headache (headache, migraine, head discomfort, sinus headache, tension headache); fatigue and lethargy (fatigue, lethargy, sluggishness); nausea and vomiting (nausea, vomiting, retching); abdominal discomfort (abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, stomach discomfort); hypotension (hypotension, orthostatic hypotension); polyuria (polyuria and pollakiuria); hypokalemia (hypokalaemia and blood potassium decreased); hyperglycemia (DM, NIDDM, glucose tolerance impaired, hyperglycaemia, blood glucose increased

[Source: FDA Clinical Reviewer's Analysis]

7.4.2 Laboratory Findings

As can be seen in Table 27, the laboratory tests with the greatest change from baseline values in the safety population of the confirmatory study were BUN/Creat, potassium, and uric acid. Mean BUN increased in all treatment groups, with the greatest increase seen in the valsartan/HCTZ group followed by the triple therapy group. Mean creatinine increased in all the HCTZ containing groups, similar to the BUN dynamics, with the greatest rise in the valsartan/HCTZ group followed by the triple therapy group. Mean uric acid increased in all the

groups with HCTZ in the regimen and was highest in the Val/HCTZ group. Mean potassium decreased in all treatment groups containing HCTZ with the greatest decrease in the HCTZ/amlodipine group. A slight increase in potassium was seen in the valsartan/amlodipine group.

Table 27: Sponsor's table of laboratory findings in the confirmatory study: Baseline, endpoint and change from baseline

Laboratory Test, units	**V/H/A 320/25/10** N=582	**V/H 320/25** N=559	**V/A 320/10** N=566	**H/A 25/10** N=561
BUN (mean, SD) mmol/L				
Baseline	5.21 (1.45)	5.13 (1.35)	5.25 (1.43)	5.24 (1.32)
Endpoint	6.25 (1.97)	6.31 (1.89)	5.66 (1.66)	5.81 (1.57)
Change from baseline	1.04 (1.76)	1.18 (1.69)	0.40 (1.45)	0.56 (1.47)
Creatinine (mean, SD) umol/L				
Baseline	85.2 (16.76)	83.3 (17.34)	84.7 (18.73)	85.0 (17.56)
Endpoint	88.9 (19.93)	88.8 (21.34)	84.5 (18.71)	85.8 (19.05)
Change from baseline	3.7 (12.62)	5.4 (14.59)	-0.1 (10.79)	0.9 (10.28)
Uric acid (mean, SD) umol/L				
Baseline	342.6 (81.40)	338.6 (84.98)	338.1 (84.65)	341.7 (79.89)
Endpoint	382.5 (96.00)	397.4 (103.51)	327.4 (85.34)	369.2 (92.05)
Change from baseline	39.9 (62.87)	58.8 (60.13)	-10.7 (53.14)	27.6 (56.77)
Potassium (mean, SD) mmol/L				
Baseline	4.28 (0.41)	4.25 (0.39)	4.28 (0.39)	4.29 (0.44)
Endpoint	4.12 (0.41)	4.17 (0.40)	4.32 (0.39)	3.91 (0.46)
Change from baseline	-0.16 (0.43)	-0.08 (0.37)	0.04 (0.37)	-0.39 (0.51)
Calcium (mean, SD) mmol/L				
Baseline	2.35 (0.11)	2.34 (0.11)	2.34 (0.11)	2.36 (0.11)
Endpoint	2.37 (0.12)	2.36 (0.11)	2.34 (0.11)	2.37 (0.11)
Change from baseline	0.02 (0.11)	0.02 (0.11)	0.00 (0.10)	0.02 (0.12)
Sodium (mean, SD) mmol/L				
Baseline	139.6 (2.54)	139.8 (2.52)	139.7 (2.59)	139.7 (2.48)
Endpoint	139.4 (3.10)	139.6 (2.98)	139.9 (2.68)	140.0 (2.91)
Change from baseline	-0.2 (2.90)	-0.3 (2.88)	0.2 (2.66)	0.3 (2.96)

Baseline is the Week 1 value, or the previous screening value if Week 1 value was not available.
Endpoint is the Week 9 laboratory value, or the previous post-baseline value if Week 9 value was not available.
A subject had to have both baseline and endpoint values to be included.

[Source: Adapted from Table 3-4, Summary of Clinical Safety, Novartis Pharmaceuticals]

Table 28 displays the number and percentage of subjects with large shifts in laboratory parameters. The parameter with the greatest numbers of subjects having shifts exceeding the pre-specified criterion was BUN, with the highest percentage of subjects in the triple therapy group (29.5%), followed by the valsartan/HCTZ (29.3%), HCTZ/amlodipine (18.5%), and finally the valsartan/amlodipine (15.8%) groups. The greatest percentages of subjects with increase in creatinine were in the triple therapy and valsartan/HCTZ groups (2.1 and 2.4%, respectively), followed by 1.8% in the HCTZ/amlodipine group and 0.7% in the valsartan/amlodipine groups. Uric acid increased in the greatest percentage of subjects in the triple therapy (2.5%) and valsartan/HCTZ (4.5) groups, and to a lesser extent in the other groups. Potassium decreased in the highest percentages of subjects in all of the HCTZ containing groups, with the highest percentage being in the non-valsartan-containing HCTZ group (19.3% in the HCTZ/amlodipine group, 6.5% in the triple therapy group, and 3.3% in the valsartan/HCTZ group). The valsartan/amlodipine group had the highest percentage of subjects with increased potassium.

Table 28: Sponsor's table of the number (%) of patients with biochemistry values exceeding pre-specified percentage changes from baseline in the confirmatory study

Laboratory Test	Criterion	V/H/A 320/25/10 N=582	V/H 320/25 N=559	V/A 320/10 N=566	H/A 25/10 N=561
Alk phos	>100% increase	2/551 (0.4)	0/529 (0.0)	0/527 (0.0)	3/526 (0.6)
SGPT (ALT)	>150% increase	4/551 (0.7)	9/529 (1.7)	6/528 (1.1)	16/526 (3.0)
SGOT (AST)	>150% increase	0/551 (0.0)	4/529 (0.8)	2/528 (0.4)	7/526 (1.3)
BUN	>50% increase	167/567 (29.5)	161/549 (29.3)	87/552 (15.8)	102/550 (18.5)
Creatinine	>50% increase	12/567 (2.1)	13/549 (2.4)	4/552 (0.7)	10/550 (1.8)
Glucose	>50% decrease	1/549 (0.2)	0/528 (0.0)	1/527 (0.2)	1/526 (0.2)
Glucose	>50% increase	12/549 (2.2)	9/528 (1.7)	8/527 (1.5)	22/526 (4.2)
Potassium	>20% decrease	37/567 (6.5)	18/549 (3.3)	2/552 (0.4)	106/550 (19.3)
Potassium	>20% increase	20/567 (3.5)	13/549 (2.4)	34/552 (6.2)	12/550 (2.2)
Sodium	>5% decrease	19/567 (3.4)	16/549 (2.9)	8/552 (1.4)	8/550 (1.5)
Bilirubin (total)	>100% increase	13/550 (2.4)	18/523 (3.4)	17/527 (3.2)	13/524 (2.5)
Chloride	>10% decrease	1/551 (0.2)	1/529 (0.2)	1/527 (0.2)	7/526 (1.3)
Chloride	>10% increase	2/551 (0.4)	0/529 (0.0)	1/527 (0.2)	0/526 (0.0)
Calcium	>10% decrease	3/551 (0.5)	6/529 (1.1)	6/527 (1.1)	9/526 (1.7)
Calcium	>10% increase	16/551 (2.9)	19/529 (3.6)	9/527 (1.7)	22/526 (4.2)
Uric Acid	>50% increase	14/551 (2.5)	24/529 (4.5)	7/527 (1.3)	8/526 (1.5)
Albumin	>25% decrease	0/552 (0.0)	0/529 (0.0)	0/527 (0.0)	0/526 (0.0)
Albumin	>50% increase	0/552 (0.0)	0/529 (0.0)	0/527 (0.0)	1/526 (0.2)
CK	>300% increase	4/551 (0.7)	6/529 (1.1)	7/529 (1.3)	6/527 (1.1)

Baseline is the Week 1 value, or the previous screening value if Week 1 value was not available.
A subject had to have both baseline and post-baseline values to be included.
N' = number of patients with baseline and post-baseline laboratory values for the specific laboratory parameter.
n = number of patients with a specified laboratory parameter abnormality.

[Source: Adapted from Table 3-5, Summary of Clinical Safety, Novartis Pharmaceuticals]

4.3 Vital Signs

Orthostatic hypotension was reported as an adverse event in 4 patients in the confirmatory study, with one of these on triple therapy, one on HCTZ/amlodipine and two on valsartan/HCTZ. 2 subjects in the valsartan/HCTZ treatment arm were discontinued due to orthostatic hypotension, one of which was serious. At all visits blood pressure was measured, and a criteria of a decrease of a minimum of 20 mmHg in systolic blood pressure or a minimum of 10 mmHg in diastolic blood pressure when a subject moved from a sitting to a standing position was used to define orthostatic blood pressure change. Two hundred and twenty-seven (227) subjects (10.1% of the total safety population of 2248) in the confirmatory study met these criteria for orthostatic hypotension at any post-baseline visit, with frequencies relatively similar across treatment groups [57 subjects (9.9%) in the triple therapy arm, 54 subjects (9.7%) in the Val/HCTZ arm, 60 subjects (10.7%) in the Val/Aml arm, and 56 subjects (10.1%) in the HCTZ/Aml arm.

7.4.4 Electrocardiograms (ECGs)

ECGs were only performed at the baseline visit with no ECG studies done after this. Thus, ECG effects of the triple combination product of approved agents were not done (please refer to individual component NDAs for ECG results of each monotherapy).

7.4.5 Special Safety Studies/Clinical Trials

Special safety studies/clinical trials were not done for this triple combination product of approved agents.

7.4.6 Immunogenicity

Given that this product is not a biologic and furthermore consists of already approved agents, immunogenicity studies were not indicated.

7.5 Other Safety Explorations

No other safety explorations were done for this triple combination product of approved agents.

7.5.1 Dose Dependency for Adverse Events

The adverse events were not adequately characterized to determine dose dependency for the adverse events.

7.5.2 Time Dependency for Adverse Events

The adverse events were not adequately characterized to determine time dependency for the adverse events.

7.5.3 Drug-Demographic Interactions

We performed demographic subgroup analysis of the safety data by pooled AE term separately for age group, gender, and race. With regard to age group, frequency of the pooled term of dizziness was greater in the older than the younger subjects, and was particularly pronounced in the triple therapy subjects [Table 29]. These descriptive statistics are limited, however, by the low numbers of subjects in the subgroups, particularly the older subgroup.

Table 29: Reviewer's table of the 15 most frequent pooled adverse events by age, pooled AE term and treatment (Confirmatory Study) in descending order by triple therapy/age<65 (in those having any randomized therapy)

AE (Preferred Term)	*V/H/A 320/25/10*		*H/A 25/10*		*V/A 320/10*		*V/H 320/25*	
	Age<65 N=491	Age ≥65 N=52	Age<65 N=432	Age ≥65 N=63	Age<65 N=454	Age ≥65 N=57	Age<65 N=466	Age ≥65 N=42
Dizziness	45 (9.2)	7 (13.5)	20 (4.6)	4 (6.3)	11 (2.4)	4 (7.0)	42 (9.0)	4 (9.5)
Edema	37 (7.5)	4 (7.7)	53 (12.3)	14 (22.2)	67 (14.8)	9 (15.8)	8 (1.7)	0 (0.0)
Headache	32 (6.5)	1 (1.9)	42 (9.7)	8 (12.7)	31 (6.8)	3 (5.3)	29 (6.2)	8 (19.0)
Dyspepsia	19 (3.9)	0 (0.0)	3 (0.7)	0 (0.0)	6 (1.3)	0 (0.0)	6 (1.3)	0 (0.0)
Fatigue/lethargy	16 (3.3)	1 (1.9)	10 (2.3)	1 (1.6)	12 (2.6)	2 (3.5)	18 (3.9)	1 (2.4)
Nausea/vomiting	16 (3.3)	0 (0.0)	14 (3.2)	1 (1.6)	12 (2.6)	4 (7.0)	10 (2.1)	0 (0.0)
Abdom discomf	12 (2.4)	2 (3.8)	8 (1.9)	0 (0.0)	10 (2.2)	2 (3.5)	15 (3.2)	0 (0.0)
Muscle spasms	12 (2.4)	1 (1.9)	3 (0.7)	2 (3.2)	7 (1.5)	1 (1.8)	10 (2.1)	0 (0.0)
Asthenia	11 (2.2)	1 (1.9)	1 (0.2)	1 (1.6)	2 (0.4)	1 (1.8)	3 (0.6)	0 (0.0)
Back pain	11 (2.2)	3 (5.8)	13 (3.0)	2 (3.2)	4 (0.9)	1 (1.8)	13 (2.8)	2 (4.8)
Nasopharyngitis	10 (2.0)	2 (3.8)	11 (2.5)	1 (1.6)	11 (2.4)	2 (3.5)	12 (2.6)	0 (0.0)
URI	9 (1.8)	1 (1.9)	6 (1.4)	0 (0.0)	7 (1.5)	1 (1.8)	9 (1.9)	3 (7.1)
Bronchitis	8 (1.6)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)
Polyuria	8 (1.6)	1 (1.9)	2 (0.5)	1 (1.6)	1 (0.2)	1 (1.8)	2 (0.4)	0 (0.0)
Diarrhea	7 (1.4)	2 (3.8)	7 (1.6)	0 (0.0)	17 (3.7)	2 (3.5)	11 (2.4)	1 (2.4)

Note - Pooling of AE is as follows: dizziness (dizziness, dizziness exertional, dizziness postural); edema (generalized oedema, gravitational oedema, oedema, peripheral oedema, pitting oedema); headache (headache, migraine, head discomfort, sinus headache, tension headache); fatigue and lethargy (fatigue, lethargy, sluggishness); nausea and vomiting (nausea, vomiting, retching); abdominal discomfort (abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, stomach discomfort); hypotension (hypotension, orthostatic hypotension); polyuria (polyuria and pollakiuria); hypokalemia (hypokalaemia and blood potassium decreased); hyperglycemia (DM, NIDDM, glucose tolerance impaired, hyperglycaemia, blood glucose increased

[Source: FDA Clinical Reviewer's Analysis]

Subgroup analysis of the pooled AE terms by both gender and race revealed no significant effects in the confirmatory study, as seen in Tables 30 and 31 below (subjects are limited to those who received any randomized therapy). These descriptive statistics are once again limited by the low numbers of subjects in the subgroups.

Table 30: Reviewer's table of the 15 most frequent pooled adverse events by gender, pooled AE term and treatment (Confirmatory Study) in descending order by triple therapy/males (in those having any randomized therapy)

AE (Preferred Term)	*V/H/A 320/25/10*		*H/A 25/10*		*V/A 320/10*		*V/H 320/25*	
	Male N=316	Female N=267	Male N=317	Female N=244	Male N=319	Female N=249	Male N=303	Female N=256
Dizziness	28 (8.9)	25 (9.4)	12 (3.8)	12 (4.9)	7 (2.2)	8 (3.2)	28 (9.2)	18 (7.0)
Headache	20 (6.3)	13 (4.9)	29 (9.1)	21 (8.6)	17 (5.3)	17 (6.8)	15 (5.0)	22 (8.6)
Edema	15 (4.7)	26 (9.7)	24 (7.6)	43 (17.6)	22 (6.9)	54 (21.7)	3 (1.0)	5 (2.0)
Dyspepsia	11 (3.5)	8 (3.0)	3 (0.9)	0 (0.0)	1 (0.3)	5 (2.0)	2 (0.7)	4 (1.6)
Back Pain	9 (2.8)	5 (1.9)	13 (4.1)	2 (0.8)	3 (0.9)	2 (0.8)	9 (3.0)	6 (2.3)
Fatigue/lethargy	8 (2.5)	9 (3.4)	7 (2.2)	4 (1.6)	5 (1.6)	9 (3.6)	11 (3.6)	8 (3.1)
URI	8 (2.5)	2 (0.7)	3 (0.9)	3 (1.2)	3 (0.9)	5 (2.0)	7 (2.3)	5 (2.0)
Asthenia	7 (2.2)	5 (1.9)	2 (0.6)	0 (0.0)	0 (0.0)	3 (1.2)	1 (0.3)	2 (0.8)
Nasopharyngitis	7 (2.2)	5 (1.9)	6 (1.9)	6 (2.5)	8 (2.5)	5 (2.0)	5 (1.7)	7 (2.7)
Polyuria	7 (2.2)	2 (0.7)	3 (0.9)	0 (0.0)	1 (0.3)	1 (0.4)	2 (0.7)	0 (0.0)
Hypokalemia	6 (1.9)	1 (0.4)	4 (1.3)	8 (3.3)	1 (0.3)	2 (0.8)	2 (0.7)	0 (0.0)
Diarrhea	6 (1.9)	3 (1.1)	4 (1.3)	3 (1.2)	13 (4.1)	6 (2.4)	5 (1.7)	7 (2.7)
Nausea/vomiting	5 (1.6)	11 (4.1)	5 (1.6)	10 (4.1)	8 (2.5)	8 (3.2)	3 (1.0)	7 (2.7)
Joint sprain	5 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Erectile Dysfunct	5 (1.6)	0 (0.0)	2 (0.6)	0 (0.0)	1 (0.3)	0 (0.0)	4 (1.3)	0 (0.0)

Note - Pooling of AE is as follows: dizziness (dizziness, dizziness exertional, dizziness postural); edema (generalized oedema, gravitational oedema, oedema, peripheral oedema, pitting oedema); headache (headache, migraine, head discomfort, sinus headache, tension headache); fatigue and lethargy (fatigue, lethargy, sluggishness); nausea and vomiting (nausea, vomiting, retching); abdominal discomfort (abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, stomach discomfort); hypotension (hypotension, orthostatic hypotension); polyuria (polyuria and pollakiuria); hypokalemia (hypokalaemia and blood potassium decreased); hyperglycemia (DM, NIDDM, glucose tolerance impaired, hyperglycaemia, blood glucose increased

[Source: FDA Clinical Reviewer's Analysis]

Table 31: Reviewer's table of the 15 most frequent pooled adverse events by race, pooled AE term and treatment (Confirmatory Study) in descending order by triple therapy/caucasians (in those having any randomized therapy)

AE (Preferred Term)	*V/H/A 320/25/10*		*H/A 25/10*		*V/A 320/10*		*V/H 320/25*	
	Cauc N=420	Black N=98	Cauc N=392	Black N=107	Cauc N=403	Black N=91	Cauc N=412	Black N=93
Dizziness	43 (10.2)	6 (6.1)	19 (4.8)	1 (0.9)	11 (2.7)	2 (2.2)	33 (8.0)	7 (7.5)
Edema	28 (6.7)	4 (4.1)	49 (12.5)	4 (3.7)	56 (13.9)	7 (7.7)	5 (1.2)	2 (2.2)
Headache	24 (5.7)	8 (8.2)	36 (9.2)	6 (5.6)	19 (4.7)	7 (7.7)	23 (5.6)	9 (9.7)
Dyspepsia	18 (4.3)	0 (0.0)	2 (0.5)	0 (0.0)	5 (1.2)	1 (1.1)	2 (0.5)	2 (2.2)
Fatigue/lethargy	13 (3.1)	3 (3.1)	10 (2.6)	0 (0.0)	10 (2.5)	2 (2.2)	15 (3.6)	3 (3.2)
Nausea/vomiting	12 (2.9)	1 (1.0)	8 (2.0)	5 (4.7)	11 (2.7)	5 (5.5)	10 (2.4)	0 (0.0)
Abdom Discomfort	11 (2.6)	2 (2.0)	5 (1.3)	2 (1.9)	10 (2.5)	1 (1.1)	6 (1.5)	8 (8.6)
Hypotension	10 (2.4)	1 (1.0)	1 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)	8 (1.9)	0 (0.0)
Nasopharyngitis	10 (2.4)	1 (1.0)	6 (1.5)	4 (3.7)	10 (2.5)	2 (2.2)	9 (2.2)	2 (2.2)
Asthenia	8 (1.9)	1 (1.0)	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.5)	1 (1.1)
Back Pain	7 (1.7)	5 (5.1)	9 (2.3)	4 (3.7)	3 (0.7)	0 (0.0)	3 (0.7)	7 (7.5)
Diarrhea	7 (1.7)	1 (1.0)	6 (1.5)	1 (0.9)	12 (3.0)	5 (5.5)	9 (2.2)	2 (2.2)
Bronchitis	6 (1.4)	1 (1.0)	1 (0.3)	1 (0.9)	0 (0.0)	0 (0.0)	4 (1.0)	0 (0.0)
Muscle Spasms	6 (1.4)	5 (5.1)	3 (0.8)	2 (1.9)	3 (0.7)	1 (1.1)	3 (0.7)	3 (3.2)
Polyuria	6 (1.4)	2 (2.0)	3 (0.8)	0 (0.0)	1 (0.2)	1 (1.1)	1 (0.2)	0 (0.0)

Note - Pooling of AE is as follows: dizziness (dizziness, dizziness exertional, dizziness postural); edema (generalized oedema, gravitational oedema, oedema, peripheral oedema, pitting oedema); headache (headache, migraine, head discomfort, sinus headache, tension headache); fatigue and lethargy (fatigue, lethargy, sluggishness); nausea and vomiting (nausea, vomiting, retching); abdominal discomfort (abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower, stomach discomfort); hypotension (hypotension, orthostatic hypotension); polyuria (polyuria and pollakiuria); hypokalemia (hypokalaemia and blood potassium decreased); hyperglycemia (DM, NIDDM, glucose tolerance impaired, hyperglycaemia, blood glucose increased

[Source: FDA Clinical Reviewer's Analysis]

7.5.4 Drug-Disease Interactions

The adverse events were not adequately characterized to determine drug-disease interactions.

7.5.5 Drug-Drug Interactions

Edema was greater in the triple therapy arm than in the non-amlodipine-containing group but was less than that seen in the two amlodipine-containing dual therapy groups.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not done for this triple combination product of approved agents. Please refer to the NDAs for each of the monotherapies (valsartan, amlodipine, and hydrochlorothiazide) for information on carcinogenicity study data for the individual components.

7.6.2 Human Reproduction and Pregnancy Data

Drugs that act on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Thus, 2 forms of contraception were a requirement for this study. 2 subjects became pregnant during the development program, both of whom were treated with triple therapy. One pregnancy resulted in the delivery of a healthy newborn and the other pregnancy was terminated. Additional information regarding pregnancy, birth, and lactation for each of the monotherapy components can be seen in their respective labeling.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric studies were not done for this triple combination product of approved agents indicated for use in adult hypertension.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdose with this triple combination product in either the clinical development program or in the sponsor's clinical safety database. Further review of the literature by us also revealed no cases of overdose.

Studies to evaluate drug abuse potential, withdrawal, and rebound were not done for this triple combination product of approved agents. Please refer to the NDAs for each of the monotherapies (valsartan, amlodipine, and hydrochlorothiazide) for such studies done for the individual components.

7.7 Additional Submissions

There were no additional submissions.

8 Postmarket Experience

8.1 Literature Search for post-marketing experience with triple combination therapy

We performed a Medline search for valsartan in combination with amlodipine and hydrochlorothiazide which resulted in the retrieval of 1 article.

1. Jackson et al. Adherence with Multiple-Combination Antihypertensive Pharmacotherapies in a US Managed Care Database. Clinical Therapeutics. 30:8 p. 1558-1563, 2008 November.

Data was collected from Jan 1997 to June 2004 from antihypertensive-naïve patients who received 2-pill pharmacotherapy with valsartan or valsartan/hydrochlorothiazide (HCTZ) in a fixed-dose combination (FDC) along with amlodipine and from those who received 3-pill therapy with valsartan, HCTZ, and amlodipine as 3 separate drug components.

MPR, or medication possession ratio, was calculated by dividing the total days' supply for the lower value in the case of individual drug components, or the number of days' supply in the case of FDC, by 365 (the number of days during the 1-year study period the medication regimen was prescribed). A general linear regression was then performed to determine the effect of treatment group on MPR, controlling for the demographic and clinical characteristics.

Data taken from 908 patients were included in the analysis (527 women, 381 men; mean age, 53.9 years; 2-pill treatment with valsartan + amlodipine, 224 patients; 2-pill treatment with valsartan/HCTZ + amlodipine, 619; and 3-pill therapy with valsartan + HCTZ + amlodipine, 65). MPR values were 75.4%, 73.1%, and 60.5%, respectively (P = 0.005). MPR improved with age (69.6% in the subset aged 18-<36 years vs 75.2% in the subset aged >64 years; P = 0.023).

These results reveal greater adherence with either 2-pill regimen compared to the 3-pill regimen, suggesting that patient compliance improves with fewer pills, thus highlighting the utility of combination therapies.

8.2 AERS Database

We were unable to tease out the experience with the triple combination of valsartan, amlodipine, and hydrochlorothiazide (i.e. those who have used the dual and monotherapy components together thus effectively using the triple combination) from the AERS database.

9 Appendices

Protocol Amendments
First protocol amendment released on 7/31/06 and the amendment included: exclusion of drugs for the treatment of attention deficit hyperactive disorder; and exclusion of potent inhibitors of CYP3A4. Second protocol amendment released 3/1907 included: language pertaining to excluding patients with MSDBP $\geq$ 120 mmHg or MSSBP $\geq$ 200 mmHg.

9.1 Literature Review/References

Review of the literature on the combination of valsartan, amlodipine, and hydrochlorothiazide yielded 1 article covering the triple combination.

1. Jackson et al. Adherence with Multiple-Combination Antihypertensive Pharmacotherapies in a US Managed Care Database. Clinical Therapeutics. 30:8 p. 1558-1563, 2008 November.

9.2 Labeling Recommendations

The reviewer's proposed changes to the labels are as follows:

On page 6 of the draft label – would recommend that the table be changed to include the most frequent adverse events in the triple therapy group, not only those that occurred at a higher incidence in the triple combination group than in any one of the dual combinations, and would include pooled terms for dizziness and edema.

b(4)

9.3 Advisory Committee Meeting

There was no advisory committee meeting for this triple combination product of approved drugs,

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/s/

Shona Pendse
4/7/2009 10:16:40 AM
MEDICAL OFFICER

Salma Lemtouni
4/7/2009 10:21:06 AM
MEDICAL OFFICER

Ququan Liu
4/23/2009 10:12:04 AM
BIOMETRICS

James Hung
4/23/2009 12:00:37 PM
BIOMETRICS

DIVISION OF CARDIOVASCULAR AND RENAL DRUG PRODUCTS
Memorandum

NDA Number:	22314
Document Type:	120 Day Safety Update
Name of Drug:	Exforge HCT
Formulation:	valsartan/amlodipine/hydrochlorothiazide
Proposed Indication:	treatment of hypertension
Sponsor:	Novartis
Date:	April 7, 2009
Reviewer:	Shona Pendse, MD, MSc

The sponsor submitted a 120 day safety update, dated October 30, 2008, for NDA 22,314. The sponsor indicated that there are two ongoing studies that were completed after the time of the NDA submission. The first of these was study AUS01, a double-blind trial designed to evaluate valsartan/amlodipine with the optional addition of open-label HCTZ, and the second of these is study VEA 2106, which was a single-dose, open-labeled, randomized, two-way crossover bioequivalence study in healthy subjects designed to evaluate whether the amlodipine component of the 160/25/10 mg valsartan/HCTZ/amlodipine fixed-combination final Market image (FMI) tablet is bioequivalent to the 10 mg amlodipine tablet administered in combination with 160 mg valsartan and 25 mg HCTZ tablets.

In the first of these studies, AUS01, 229 patients were randomized into the study, and of these, 35 withdrew from the study prior to completing participation, 19 in the intensive blood pressure treatment arm and 16 in the standard treatment arm. The most common reasons for discontinuation were withdrawal of consent, adverse events, and loss to follow-up. A total of 128 patients received triple therapy in the 2 arms combined. Dizziness, peripheral edema and URI were the most frequently reported adverse events in the triple therapy patients. No deaths were reported in the study. Serious adverse events were reported for 6 randomized patients, 3 of whom were on triple therapy. The first of these had pancreatitis and acute cholecystitis and underwent cholecystectomy, the second presented with dizziness and was found to have a thyroid neoplasm and a goiter, resulting in thyroidectomy, and the third patient presented with head injury from a fall and was found to have atrial fibrillation and hypotension. There were 9 randomized patients (3.9%) in total that experienced adverse events resulting in discontinuation from the study, 6 in the intensive treatment arm and 3 in the standard treatment arm. Most AEs causing discontinuation were found in only one patient. The only adverse event that resulted in discontinuation for more than one patient was edema, which occurred in 1 patient in each arm of the study (intensive and standard blood pressure treatment).

In the second of these studies, the bioequivalence study VEA 2106, 26 subjects were enrolled in the study and received at least one dose of the study drug. Of these subjects, 23 completed the study and 3 subjects were withdrawn during the baseline of Period 2. Two of these subjects had abnormal safety lab results and one subject was excluded due to a protocol violation (in dietary restrictions). The overall incidence of subjects experiencing at least one AE was similar across the FMI and free combination treatment groups. 11 of the 26 subjects (42.3%) reported 1 or more adverse events during the study. A total of 18 adverse events were reported during the study. The most common

adverse events were headache (5/18; 27.8%), followed by dizziness (2/18; 11.1%). Three AE's were deemed related to study drug and all of these were mild in severity: one of these was asthenia and the other two were reports of dizziness. None of the AE's in this study resulted in discontinuation. There were no deaths or serious adverse events during this study. With regard to laboratory test results, two subjects had elevated serum bilirubin according to the sponsor, and 1 subject had low WBC. There were also 2 subjects that were withdrawn due to laboratory abnormalities. The first of these subjects presented, at baseline of Period 2 on 18-April-2008 after the 14 day washout period with elevated ALT at 110 U/L (ref range 10-67), AST at 352 U/L (ref range: 14-48), CK at 25,956 U/L (ref range: 43-350), LDH elevated at 755 U/L (ref range: 131-249) and was withdrawn from the study. He was asymptomatic but upon questioning, reported physical activity. Upon return for their end of study visit on 26-April-2008, the ALT, AST, and LDH results were within normal ranges while the CK levels were still slightly elevated (598 U/L; 1.7x the ULN). This subject had entered the study with normal levels of ALT, AST, CK and LDH.
The second subject presented at baseline of Period 2 on 18-April-2008 after the 14 day washout with elevated AST at 146 U/L (ref range: 14-48), CK of 9087 U/L (ref range: 43-350), LDH of 348 U/L (ref range: 131-249) and was withdrawn from the study. He was also asymptomatic and upon questioning, reported physical activity. Upon return for their end of study visit on 26-April-2008, the AST, and LDH results were within normal ranges. The CK levels were still slightly elevated (626 U/L; 1.8x the ULN). This subject had also entered the study with normal levels of AST, CK and LDH. Both subjects were deemed to have laboratory abnormalities related to exercise.

The sponsors also performed a literature search for articles on the combination of valsartan, hydrochlorothiazide and amlodipine and retrieved one article reporting safety data from study VAA A2403 which has been included in the NDA submission for 22314.

Reviewer's comment: There are no significant new safety concerns for valsartan/HCTZ/amlodipine that would preclude an approval action.

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/s/

Shona Pendse
4/9/2009 07:40:44 AM
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