CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021990Orig1s003

Trade Name: EXFORGE

Generic Name: amlodipine and valsartan

Sponsor: Novartis.

Approval Date: July 23, 2008

Indication: Exforge is indicated for the treatment of hypertension

- In patients not adequately controlled on monotherapy
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

CENTER FOR DRUG EVALUATION AND RESEARCH

021990Orig1s003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-990/S-003

Novartis Pharmaceuticals Corporation
Attention: Ms. Donna Vivelo
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Vivelo:

Please refer to your supplemental new drug application (sNDA) dated September 24, 2007, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exforge (amlodipine and valsartan) 5/160, 10/160, 5/320, and 10/320 mg Tablets.

We acknowledge receipt of your submissions dated October 5, 2007 and January 24 and 29, March 31, May 30, June 27, July 3, 15 and 21, 2008.

This supplemental new drug application provides for the use of Exforge Tablets as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (text for the package insert and text for the patient package insert). These revisions are terms of the approval of this application.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-990/S-003."

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

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

/s/

Norman Stockbridge

7/23/2008 04:13:45 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Exforge safely and effectively. See full prescribing information for Exforge.

Exforge® (amlodipine and valsartan) Tablets
Initial U.S. Approval: 2007

WARNING: AVOID USE IN PREGNANCY
See full prescribing information for complete boxed warning.
When pregnancy is detected, discontinue Exforge as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. (5.1)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	7/2008
Dosage and Administration, Initial Therapy (2.4)	7/2008

----------INDICATIONS AND USAGE----------

Exforge® is the combination tablet of amlodipine, a dihydropyridine calcium channel blocker (DHP CCB), and valsartan, an angiotensin II receptor blocker (ARB). Exforge is indicated for the treatment of hypertension:

- In patients not adequately controlled on monotherapy (1)
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals (1).

----------DOSAGE AND ADMINISTRATION----------

General Considerations:

- Majority of effect attained within 2 weeks (2.1)
- May be administered with other antihypertensive agents (2.1)

Hypertension

- May be used as add-on therapy for patients not controlled on monotherapy (2.2)
- Patients who experience dose-limiting adverse reactions on monotherapy may be switched to Exforge containing a lower dose of that component (2.2)
- May be substituted for titrated components (2.3)
- When used as initial therapy: Initiate with 5/160 mg, then titrate upwards as necessary to a maximum of 10/320 mg once daily (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets (amlodipine/valsartan mg): 5/160, 10/160, 5/320, 10/320 (3)

----------WARNINGS AND PRECAUTIONS----------

- Avoid fetal or neonatal exposure (5.1)
- Assess for hypotension. (5.2)
- Warn patients with severe obstructive coronary artery disease about the risk of myocardial infarction or increased angina (5.3)
- Titrate slowly in patients with impaired hepatic (5.4) or severely impaired renal (5.5) function

----------ADVERSE REACTIONS----------

In placebo-controlled clinical trials, discontinuation due to side effects occurred in 1.8% of patients in 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 and vertigo. The adverse experiences that occurred in clinical trials (≥2% of patients) at a higher incidence than placebo included peripheral edema, nasopharyngitis, upper respiratory tract infection and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------

Start amlodipine or add amlodipine at 2.5 mg in patients ≥ 75 years old or in patients with hepatic impairment. (8.5)

Nursing Mothers: Choose breastfeeding or Exforge therapy, but not both. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: July 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: AVOID USE IN PREGNANCY

When pregnancy is detected, discontinue Exforge® as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. [*See Warnings and Precautions (5.1)*]

1 INDICATIONS AND USAGE

1.1 Hypertension

Exforge (amlodipine and valsartan) is indicated for the treatment of hypertension.

Exforge may be used in patients whose blood pressure is not adequately controlled on either monotherapy.

Exforge may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.

The choice of Exforge as initial therapy for hypertension should be based on an assessment of potential benefits and risks including whether the patient is likely to tolerate the lowest dose of Exforge.

Patients with stage 2 hypertension (moderate or severe) are at a relatively higher risk for cardiovascular events (such as strokes, heart attacks, and heart failure), kidney failure and vision problems, so prompt treatment is clinically relevant. The decision to use a combination as initial therapy should be individualized and should be shaped by considerations such as baseline blood pressure, the target goal and the incremental likelihood of achieving goal with a combination compared to monotherapy. Individual blood pressure goals may vary based upon the patient's risk.

Data from the high-dose multifactorial study [*see Clinical Studies (14)*] provide estimates of the probability of reaching a blood pressure goal with Exforge compared to amlodipine or valsartan monotherapy. The figures below provide estimates of the likelihood of achieving systolic or diastolic blood pressure control with Exforge 10/320 mg, based upon baseline systolic or diastolic blood pressure. The curve of each treatment group was estimated by logistic regression modeling. The estimated likelihood at the right tail of each curve is less reliable due to small numbers of subjects with high baseline blood pressures.

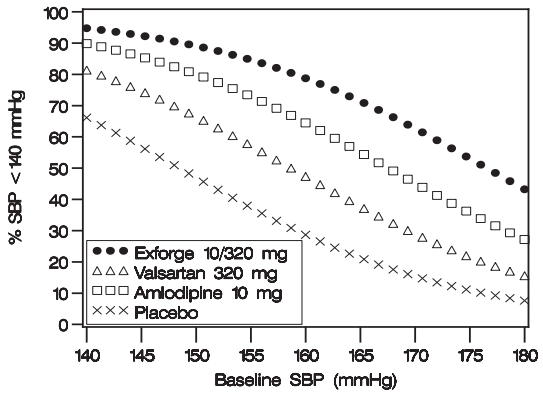


Figure 1: Probability of Achieving Systolic Blood Pressure <140 mmHg at Week 8

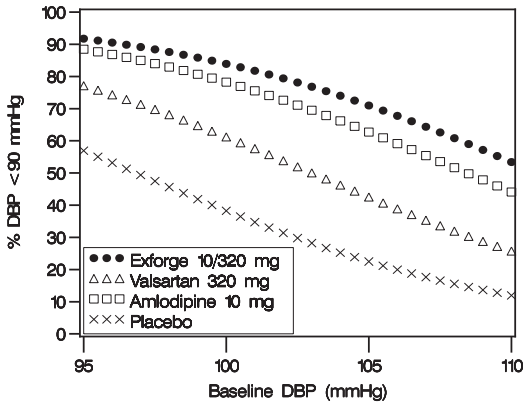


Figure 2: Probability of Achieving Diastolic Blood Pressure <90 mmHg at Week 8

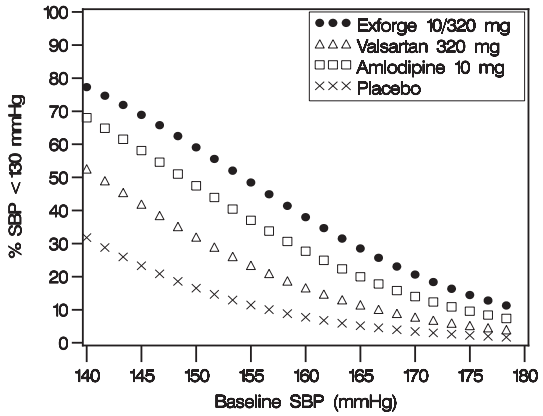


Figure 3: Probability of Achieving Systolic Blood Pressure <130 mmHg at Week 8

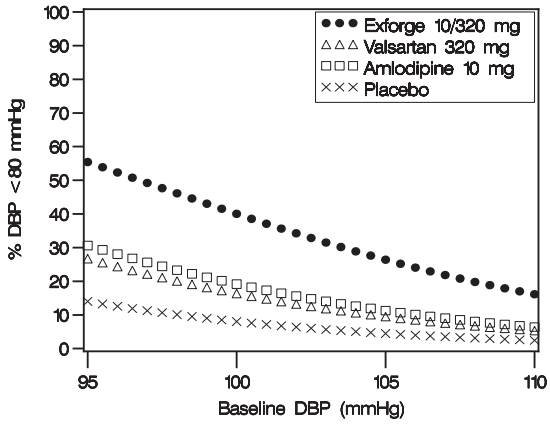


Figure 4: Probability of Achieving Diastolic Blood Pressure <80 mmHg at Week 8

For example, a patient with a baseline blood pressure of 160/100 mmHg has about a 67% likelihood of achieving a goal of <140 mmHg (systolic) and 80% likelihood of achieving <90 mmHg (diastolic) on amlodipine alone, and the likelihood of achieving these goals on valsartan alone is about 47% (systolic) or 62% (diastolic). The likelihood of achieving these goals on Exforge rises to about 80% (systolic) or 85% (diastolic). The likelihood of achieving these goals on placebo is about 28% (systolic) or 37% (diastolic).

2. DOSAGE AND ADMINISTRATION

2.1 General Considerations

Amlodipine is an effective treatment of hypertension in once daily doses of 2.5 mg to 10 mg while valsartan is effective in doses of 80 mg to 320 mg. In clinical trials with once daily Exforge (amlodipine and valsartan) using amlodipine doses of 5 mg to 10 mg and valsartan doses of 160 mg to 320 mg, the antihypertensive effects increased with increasing doses.

The hazards [*see Warnings and Precautions(5)*] of valsartan are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter [*see Adverse Reactions (6)*.]

The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 10/320 mg tablet once daily as needed to control blood pressure [See *Clinical Studies* (14)].

Exforge may be administered with or without food.

Exforge may be administered with other antihypertensive agents.

Elderly patients: Because of decreased clearance of amlodipine, therapy should usually be initiated at 2.5 mg.

Renal Impairment: No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.

Hepatic Impairment: No initial dosage adjustment is required for patients with mild or moderate liver insufficiency. Titrate slowly in patients with hepatic impairment.

2.2 Add-on Therapy

A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine calcium-channel blocker) alone or with valsartan (or another angiotensin II receptor blocker) alone may be switched to combination therapy with Exforge.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to Exforge containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. The clinical response to Exforge should be subsequently evaluated and if blood pressure remains uncontrolled after 3 to 4 weeks of therapy, the dose may be titrated up to a maximum of 10/320 mg.

2.3 Replacement Therapy

For convenience, patients receiving amlodipine and valsartan from separate tablets may instead wish to receive tablets of Exforge containing the same component doses.

2.4 Initial Therapy

A patient may be initiated on Exforge if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose is Exforge 5/160 mg once daily in patients who are not volume-depleted.

3 DOSAGE FORMS AND STRENGTHS

5/160 mg tablets, debossed with NVR/ECE (side 1/side 2)

10/160 mg tablets, debossed with NVR/UIC

5/320 mg tablets, debossed with NVR/CSF

10/320 mg tablets, debossed with NVR/LUF

5 WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality

Exforge can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Drugs that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death *[see Use in Specific Populations (8.1)]*.

5.2 Hypotension

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Exforge® (amlodipine and valsartan) in placebo-controlled studies. In patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. Volume depletion should be corrected prior to administration of Exforge. Treatment with Exforge should start under close medical supervision.

Initiate therapy cautiously in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering amlodipine, particularly in patients with severe aortic stenosis.

If excessive hypotension occurs with Exforge, the patient should be placed in a supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.3 Risk of Myocardial Infarction or Increased Angina

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

5.4 Impaired Hepatic Function

Studies with Amlodipine: Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t½) is 56 hours in patients with impaired hepatic function, therefore, caution should be exercised when administering amlodipine to patients with severe hepatic impairment.

Studies with Valsartan: As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients.

5.5 Impaired Renal Function - Hypertension

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may occur particularly in volume depleted patients. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan.

5.6 Congestive Heart Failure

Studies with Amlodipine: In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Studies with Valsartan: Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not

reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Studies with Exforge:

Exforge (amlodipine and valsartan) has been evaluated for safety in over 2,600 patients with hypertension; over 1,440 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least one year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, or race. In placebo-controlled clinical trials, discontinuation due to side effects occurred in 1.8% of patients in 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%).

The adverse reactions that occurred in placebo-controlled clinical trials in at least 2% of patients treated with Exforge but at a higher incidence in amlodipine/valsartan patients (n=1,437) than placebo (n=337) included peripheral edema (5.4% vs. 3.0%), nasopharyngitis (4.3% vs. 1.8%), upper respiratory tract infection (2.9% vs 2.1%) and dizziness (2.1% vs 0.9%).

Orthostatic events (orthostatic hypotension and postural dizziness) were seen in less than 1% of patients.

Other adverse reactions that occurred in placebo-controlled clinical trials with Exforge (≥ 0.2%) are listed below. It cannot be determined whether these events were causally related to Exforge.

Blood and Lymphatic System Disorders: Lymphadenopathy

Cardiac Disorders: Palpitations, tachycardia

Ear and Labyrinth Disorders: Ear pain

Gastrointestinal Disorders: Diarrhea, nausea, constipation, dyspepsia, abdominal pain, abdominal pain upper, gastritis, vomiting, abdominal discomfort, abdominal distention, dry mouth, colitis

General Disorders and Administration Site Conditions: Fatigue, chest pain, asthenia, pitting edema, pyrexia, edema

Immune System Disorders: seasonal allergies

Infections and Infestations: Nasopharyngitis, sinusitis, bronchitis, pharyngitis, gastroenteritis, pharyngotonsillitis, bronchitis acute, tonsillitis~~,~~

Injury and Poisoning: Epicondylitis, joint sprain, limb injury~~, ***Metabolism and Nutrition Disorders***: Gout, non-insulin-dependent diabetes mellitus, hypercholesterolemia~~

Metabolism and Nutrition Disorders: Gout, non-insulin dependent diabetes mellitus, hypercholesterolemia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, muscle spasms, pain in extremity, myalgia, osteoarthritis, joint swelling, musculoskeletal chest pain

Nervous System Disorders: Headache, sciatica, parasthesia, cerviocobrachial syndrome, carpal tunnel syndrome, hypoaesthesia, sinus headache, somnolence

Psychiatric Disorders: Insomnia, anxiety, depression

Renal and Urinary Disorders: Hematuria, nephrolithiasis, pollakiuria

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Cough, pharyngolaryngeal pain, sinus congestion, dyspnea, epistaxis, productive cough, dysphonia, nasal congestion

Skin and Subcutaneous Tissue Disorders: Pruritus, rash, hyperhidrosis, eczema, erythema

Vascular Disorders: Flushing, hot flush

Isolated cases of the following clinically notable adverse reactions were also observed in clinical trials: exanthema, syncope, visual disturbance, hypersensitivity, tinnitus, and hypotension.

Studies with Amlodipine:

Norvasc® has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. Other adverse events that have been reported <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain were:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, postural hypotension, vasculitis

Central and Peripheral Nervous System: neuropathy peripheral, tremor

Gastrointestinal: anorexia, dysphagia, pancreatitis, gingival hyperplasia

General: allergic reaction, hot flushes, malaise, rigors, weight gain, weight loss

Musculoskeletal System: arthrosis, muscle cramps

Psychiatric: sexual dysfunction (male and female), nervousness, abnormal dreams, depersonalization

Respiratory System: dyspnea

Skin and Appendages: angioedema, erythema multiforme, rash erythematous, rash maculopapular

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus

Urinary System: micturation frequency, micturation disorder, nocturia

Autonomic Nervous System: sweating increased

Metabolic and Nutritional: hyperglycemia, thirst

Hemopoietic: leukopenia, purpura, thrombocytopenia

Other events reported with amlodipine at a frequency of ≤0.1% of patients include: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Adverse reactions reported for amlodipine for indications other than hypertension may be found in the prescribing information for Norvasc®.

Studies with Valsartan:

Diovan® has been evaluated for safety in more than 4,000 hypertensive patients in clinical trials. In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or

placebo (1.5%). In a 129 patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p<0.001$).

Other adverse reactions, not listed above, occurring in >0.2% of patients in controlled clinical trials with valsartan are:

Body as a Whole: allergic reaction, asthenia

Musculoskeletal: muscle cramps

Neurologic and Psychiatric: paresthesia

Respiratory: sinusitis, pharyngitis

Urogenital: Impotence

Other reported events seen less frequently in clinical trials were: angioedema.

Adverse reactions reported for valsartan for indications other than hypertension may be found in the prescribing information for Diovan.

6.2 Postmarketing Experience

Amlodipine: Gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.

Valsartan: The following additional adverse reactions have been reported in postmarketing experience with valsartan:

Blood and Lymphatic: There are very rare reports of thrombocytopenia.

Hypersensitivity: There are rare reports of angioedema.

Digestive: Elevated liver enzymes and very rare reports of hepatitis

Renal: Impaired renal function

Clinical Laboratory Tests: Hyperkalemia

Dermatologic: Alopecia

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

7 DRUG INTERACTIONS

7.1 Drug/Drug Interactions

No drug interaction studies have been conducted with Exforge and other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below:

Studies with Amlodipine

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Maalox® (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single 100 mg dose of sildenafil (Viagra®**) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Studies with Valsartan

No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Warfarin: Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

7.2 CYP 450 Interactions

The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

7.3 Drug/Food Interactions

Studies with Exforge

The bioavailabilities of amlodipine and valsartan are not altered by the co-administration of food.

7.4 Clinical Laboratory Findings

Creatinine: In hypertensive patients, greater than 50% increases in creatinine occurred in 0.4% of patients receiving Exforge and 0.6% receiving placebo. In heart failure patients, greater than 50% increases in creatinine were observed in 3.9% of valsartan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Exforge-treated patients.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 2.8% of Exforge-treated patients compared to 3.4% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10% of valsartan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In hypertensive patients, greater than 50% increases in BUN were observed in 5.5% of Exforge-treated patients compared to 4.7% of placebo-treated patients. In heart failure patients, greater than 50% increases in BUN were observed in 16.6% of valsartan-treated patients compared to 6.3% of placebo-treated patients.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [~~see~~ see *Warnings and Precautions (5.1)*]

Exforge, like other drugs that act on the renin angiotensin system, can cause fetal and neonatal morbidity and death when used during the second or third trimester of pregnancy. Exforge can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In a retrospective study, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin angiotensin system, was associated with a potential risk of birth defects.

When pregnancy occurs in a patient using Exforge, the physician should discontinue Exforge treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Exforge (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.

In rare cases when another antihypertensive agent cannot be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Exforge treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to Exforge should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

Healthcare professionals who prescribe drugs acting directly on the renin angiotensin system should counsel women of childbearing potential about the risks of these agents during pregnancy. *[~~see~~ see Nonclincial Toxicology (13.2)]*.

8.2 Labor and Delivery

The effect of Exforge on labor and delivery has not been studied.

8.3 Nursing Mothers

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered.

It is not known whether valsartan is excreted in human milk. Valsartan was excreted into the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from Exforge, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of Exforge in pediatric patients have not been established.

8.5 Geriatric Use

In controlled clinical trials, 323 (22.5%) hypertensive patients treated with Exforge were ≥65 years and 79 (5.5%) were ≥75 years. No overall differences in the efficacy or safety of Exforge was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Amlodipine: Clinical studies of amlodipine besylate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required [see *Dosage and Administration*~~*DOSAGE AND ADMINISTRATION (2.1)*~~].

Valsartan: In the controlled clinical trials of valsartan, 1,214 (36.2%) of hypertensive patients treated with valsartan were ≥65 years and 265 (7.9%) were ≥75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

~~Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 53% (2,596) of the 4,909 patients treated with valsartan and 51% (2,515) of the 4,885 patients treated with valsartan + captopril were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients in either trial.~~

10. OVERDOSAGE

Information on Amlodipine

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose

has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae was noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Information on Valsartan

Limited data are available related to overdosage in humans. The most likely effect of overdose with valsartan would be peripheral vasodilation, hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

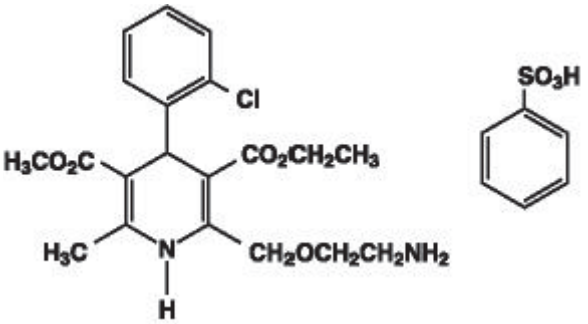
Valsartan is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for the salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

11. DESCRIPTION

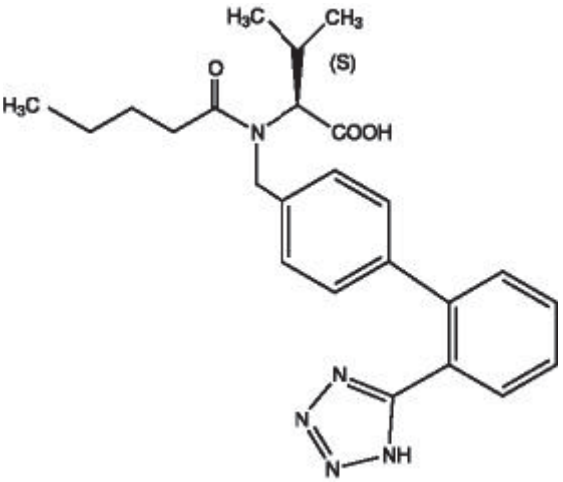
Exforge is a fixed combination of amlodipine and valsartan.

Exforge contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl(4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate; its structural formula is



Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and its molecular weight is 567.1.

Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT_1 receptor subtype. Valsartan is a white to practically white fine powder, soluble in ethanol and methanol and slightly soluble in water. Valsartan's chemical name is N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine; its structural formula is



Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5.

Exforge tablets are formulated in four 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 providing for the following available combinations: 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg.

The inactive ingredients for all strengths of the tablets are colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Additionally the 5/320 mg and 10/320 mg strengths contain iron oxide yellow and sodium starch glycolate. The film coating contains hypromellose, iron oxides, polyethylene glycol, talc and titanium dioxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Valsartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one-200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

12.2 Pharmacodynamics

Amlodipine

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressure (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects of electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Amlodipine has indications other than hypertension which can be found in the Norvasc®* package insert.

Valsartan

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic blood pressure, usually with little or no orthostatic change.

Valsartan has indications other than hypertension which can be found in the Diovan® package insert.

Exforge

Exforge has been shown to be effective in lowering blood pressure. Both amlodipine and valsartan lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complementary mechanisms.

12.3 Pharmacokinetics

Amlodipine

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of amlodipine alone. Absolute bioavailability has been estimated to be between 64% and 90%. The bioavailability of amlodipine is not altered by the presence of food.

The apparent volume of distribution of amlodipine is 21 L/kg. Approximately 93% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine.

Elimination of amlodipine from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Steady state plasma levels of amlodipine are reached after 7-8 days of consecutive daily dosing.

Valsartan

Following oral administration of valsartan alone peak plasma concentrations of valsartan are reached in 2-4 hours. Absolute bioavailability is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%.

The steady state volume of distribution of valsartan after intravenous administration is 17 L indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Valsartan shows bi-exponential decay kinetics following intravenous administration with an average elimination half-life of about 6 hours. The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isoenzymes.

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Exforge

Following oral administration of Exforge in normal healthy adults, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of valsartan and amlodipine from Exforge are the same as when administered as individual tablets.

Special Populations

Geriatric

~~***Studies with Amlodipine***~~

Studies with Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%-60%; therefore a lower initial dose of amlodipine may be required.

~~***Studies with Valsartan***~~

Studies with Valsartan: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary.

Gender

~~***Studies with Valsartan***~~

Studies with Valsartan: Pharmacokinetics of valsartan does not differ significantly between males and females.

Renal Insufficiency

~~***Studies with Amlodipine***~~

Studies with Amlodipine: The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

~~***Studies with Valsartan***~~

Studies with Valsartan: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan.

Hepatic Insufficiency

~~***Studies with Amlodipine***~~

Studies with Amlodipine: Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40%-60%; therefore, a lower initial dose of amlodipine may be required.

~~***Studies with Valsartan***~~

Studies with Valsartan: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

Studies with Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on mg/m^2 basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m^2 basis, about two and a half times the MRHD. (Calculations based on a 60 kg patient.)

Mutagenicity studies conducted with amlodipine maleate revealed no drug-related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses of up to 10 mg amlodipine/kg/day (about 10 times the MRHD of 10 mg/day on a mg/m^2 basis).

Studies with Valsartan

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at concentrations calculated to provide doses of up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.4 and 6 times, respectively, the MRHD of 320 mg/day on a mg/m^2 basis. (Calculations based on a 60 kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli, a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with Chinese hamster ovary cells, and a rat micronucleus test.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses of up to 200 mg/kg/day. This dose is about 6 times the maximum recommended human dose on a mg/m^2 basis.

Studies with Amlodipine

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses of up to 10 mg amlodipine/kg/day (respectively, about 10 and 20 times the maximum recommended human dose [MRHD] of 10 mg amlodipine on a mg/m^2 basis) during their respective periods of major organogenesis. (Calculations based on a patient weight of 60 kg.) However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) for rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies with Valsartan

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses of up to 600 mg/kg/day and to pregnant rabbits at oral doses of up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with

maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits, respectively, are about 9, 6 and 0.1 times the MRHD of 320 mg/day on a mg/m^2 basis. (Calculations based on a patient weight of 60 kg.)

Studies with Amlodipine Besylate and Valsartan

In the oral embryo-fetal development study in rats using amlodipine besylate plus valsartan at doses equivalent to 5 mg/kg/day amlodipine plus 80 mg/kg/day valsartan, 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan, and 20 mg/kg/day amlodipine plus 320 mg/kg/day valsartan, treatment-related maternal and fetal effects (developmental delays and alterations noted in the presence of significant maternal toxicity) were noted with the high dose combination. The no-observed-adverse-effect level (NOAEL) for embryo-fetal effects was 10 mg/kg/day amlodipine plus 160 mg/kg/day valsartan. On a systemic exposure [$AUC_{(0-\infty)}$] basis, these doses are, respectively, 4.3 and 2.7 times the systemic exposure [$AUC_{(0-\infty)}$] in humans receiving the MRHD (10/320 mg/60 kg).

14 CLINICAL STUDIES

Exforge was studied in 2 placebo-controlled and 4 active-controlled trials in hypertensive patients. In a double-blind, placebo controlled study, a total of 1012 patients with mild-to-moderate hypertension received treatments of three combinations of amlodipine and valsartan (5/80, 5/160, 5/320 mg) or amlodipine alone (5 mg), valsartan alone (80, 160, or 320 mg) or placebo. All doses with the exception of the 5/320 mg dose were initiated at the randomized dose. The high dose was titrated to that dose after a week at a dose of 5/160 mg. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.

Table 1: Effect of Exforge on Sitting Diastolic Blood Pressure

Amlodipine dosage	Valsartan dosage							
	0 mg		80 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-6.4	---	-9.5	-3.1	-10.9	-4.5	-13.2	-6.7
5 mg	-11.1	-4.7	-14.2	-7.8	-14.0	-7.6	-15.7	-9.3

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Diastolic Blood Pressure. Mean baseline diastolic BP was 99.3 mmHg.

Table 2: Effect of Exforge on Sitting Systolic Blood Pressure

Amlodipine dosage	Valsartan dosage							
	0 mg		80 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-6.2	---	-12.9	-6.8	-14.3	-8.2	-16.3	-10.1
5 mg	-14.8	-8.6	-20.7	-14.5	-19.4	-13.2	-22.4	-16.2

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Systolic Blood Pressure. Mean baseline systolic BP was 152.8 mmHg.

In a double-blind, placebo controlled study, a total of 1246 patients with mild to moderate hypertension received treatments of two combinations of amlodipine and valsartan (10/160, 10/320 mg) or amlodipine alone (10 mg), valsartan alone (160 or 320 mg) or placebo. With the exception of the 10/320 mg dose, treatment was initiated at the randomized dose. The high dose was initiated at a dose of 5/160 mg and titrated to the

randomized dose after 1 week. At week 8, the combination treatments were statistically significantly superior to their monotherapy components in reduction of diastolic and systolic blood pressures.

Table 3: Effect of Exforge on Sitting Diastolic Blood Pressure

Amlodipine dosage	Valsartan dosage					
	0 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-8.2	---	-12.8	- 4.5	-12.8	-4.5
10 mg	-15.0	-6.7	- 17.2	- 9.0	-18.1	-9.9

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Diastolic Blood Pressure. Mean baseline diastolic BP was 99.1 mmHg.

Table 4: Effect of Exforge on Sitting Systolic Blood Pressure

Amlodipine dosage	Valsartan dosage					
	0 mg		160 mg		320 mg	
	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted	Mean Change*	Placebo-subtracted
0 mg	-11.0	---	-18.1	-7.0	-18.5	-7.5
10 mg	-22.2	-11.2	-26.6	-15.5	-26.9	-15.9

*Mean Change and Placebo-Subtracted Mean Change from Baseline (mmHg) at Week 8 in Sitting Systolic Blood Pressure. Mean baseline systolic BP was 156.7 mmHg.

In a double-blind, active-controlled study, a total of 947 patients with mild to moderate hypertension who were not adequately controlled on valsartan 160 mg received treatments of two combinations of amlodipine and valsartan (10/160, 5/160 mg), or valsartan alone (160 mg). At week 8, the combination treatments were statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Table 5: Effect of Exforge on Sitting Diastolic/Systolic Blood Pressure

Treatment Group	Diastolic BP		Systolic BP	
	Mean change*	Treatment Difference**	Mean change*	Treatment Difference**
Exforge 10/160 mg	-11.4	-4.8	-13.9	-5.7
Exforge 5/160 mg	-9.6	-3.1	-12.0	-3.9
Valsartan 160 mg	-6.6	---	-8.2	---

*Mean Change from Baseline at Week 8 in Sitting Diastolic/Systolic Blood Pressure. Mean baseline BP was 149.5/ 96.5 (systolic/diastolic) mmHg

**Treatment Difference = difference in mean BP reduction between Exforge and the control group (Valsartan 160 mg)

In a double-blind, active-controlled study, a total of 944 patients with mild to moderate hypertension who were not adequately controlled on amlodipine 10 mg received a combination of amlodipine and valsartan (10/160 mg), or amlodipine alone (10 mg). At week 8, the combination treatment was statistically significantly superior to the monotherapy component in reduction of diastolic and systolic blood pressures.

Table 6: Effect of Exforge on Sitting Diastolic/Systolic Blood Pressure

Treatment Group	Diastolic BP		Systolic BP	
	Mean change*	Treatment Difference**	Mean change*	Treatment Difference**
Exforge 10/160 mg	-11.8	-1.8	-12.7	-1.9
Amlodipine 10 mg	-10.0	---	-10.8	---

*Mean Change from Baseline at Week 8 in Sitting Diastolic/Systolic Blood Pressure. Mean baseline BP was 147.0/ 95.1 (systolic/diastolic) mmHg

**Treatment Difference = difference in mean BP reduction between Exforge and the control group (Amlodipine 10 mg)

Exforge was also evaluated for safety in a 6-week, double-blind, active-controlled trial of 130 hypertensive patients with severe hypertension (mean baseline BP of 171/113 mmHg). Adverse events were similar in patients with severe hypertension and mild/moderate hypertension treated with Exforge.

A wide age range of the adult population, including the elderly was studied (range 19-92 years, mean 54.7 years). Women comprised almost half of the studied population (47.3%). Of the patients in the studied Exforge group, 87.6% were Caucasian. Black and Asian patients each represented approximately 4% of the population in the studied Exforge group.

Two additional double-blind, active-controlled studies were conducted in which Exforge was administered as initial therapy. In one study, a total of 572 Black patients with moderate to severe hypertension were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 12 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by optional titration to 10/320 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by optional titration to 10 mg for 4 weeks and optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 8 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.7/2.8 mmHg.

In the other study of similar design, a total of 646 patients with moderate to severe hypertension (MSSBP of ≥ 160 mmHg and <200 mmHg) were randomized to receive either combination amlodipine/valsartan or amlodipine monotherapy for 8 weeks. The initial dose of amlodipine/valsartan was 5/160 mg for 2 weeks with forced titration to 10/160 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. The initial dose of amlodipine was 5 mg for 2 weeks with forced titration to 10 mg for 2 weeks, followed by the optional addition of HCTZ 12.5 mg for 4 weeks. At the primary endpoint of 4 weeks, the treatment difference between amlodipine/valsartan and amlodipine was 6.6/3.9 mmHg.

16 HOW SUPPLIED/STORAGE AND HANDLING

Exforge is available as non-scored tablets containing amlodipine besylate equivalent to 5 mg, or 10 mg of amlodipine free-base with valsartan 160 mg or 320 mg, providing for the following available combinations: 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg.

All strengths are packaged in bottles of 30 and 90 count, and unit dose blister packages.

5/160 mg Tablets - dark yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with "NVR" on one side and "ECE" on the other side.

Bottles of 30 NDC # 0078-0488-15

Bottles of 90 NDC # 0078-0488-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0488-35

10/160 mg Tablets - light yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with "NVR" on one side and "UIC" on the other side.

Bottles of 30 NDC # 0078-0489-15

Bottles of 90 NDC # 0078-0489-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0489-35

5/320 mg Tablets - very dark yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with "NVR" on one side and "CSF" on the other side.

Bottles of 30 NDC # 0078-0490-15

Bottles of 90 NDC # 0078-0490-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0490-35

10/320 mg Tablets - dark yellow, ovaloid shaped, film coated tablet with beveled edge, debossed with "NVR" on one side and "LUF" on the other side.

Bottles of 30 NDC # 0078-0491-15

Bottles of 90 NDC # 0078-0491-34

Unit Dose 100 tablets (10 X 10 tablets blister cards) NDC # 0078-0491-35

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Protect from moisture.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Pregnancy: Female patients of childbearing age should be told that use of drugs like valsartan that act on the renin-angiotensin system can cause serious problems in the fetus and infant including: low blood pressure, poor development of skull bones, kidney failure and death. Discuss other treatment options with female patients planning to become pregnant. Women using Exforge who become pregnant should notify their physicians as soon as possible.

17.2 FDA-Approved Patient Labeling ~~[Note to Division: PPI will be re-inserted]~~

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Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

July 2008

PATIENT INFORMATION

EXFORGE (X-phorj)
(amlodipine and valsartan)
Tablets

Read the Patient Information that comes with EXFORGE before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about EXFORGE, ask your doctor or pharmacist.

What is the most important information I should know about EXFORGE?

If you become pregnant, stop taking EXFORGE and call your doctor right away. EXFORGE can harm an unborn baby causing injury and even death. If you plan to become pregnant, talk to your doctor about other treatment options to lower your blood pressure before taking EXFORGE.

What is EXFORGE?

EXFORGE contains two prescription medicines:

1. amlodipine, a calcium channel blocker
2. valsartan, an angiotensin receptor blocker (ARB).

EXFORGE may be used to lower high blood pressure (hypertension) in adults-

- when one medicine to lower your high blood pressure is not enough
- as the first medicine to lower high blood pressure if your doctor decides you are likely to need more than one medicine.

EXFORGE has not been studied in children under 18 years of age.

What should I tell my doctor before taking EXFORGE?

Tell your doctor about all of your medical conditions, including if you:

- **are pregnant or plan to become pregnant.** See "What is the most important information I should know about EXFORGE?"
- **are breast-feeding or plan to breast-feed.** EXFORGE may pass into your milk. Do not breast-feed while you are taking EXFORGE.
- have heart problems
- have liver problems
- have kidney problems
- are vomiting or having a lot of diarrhea

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines and EXFORGE could affect each other, causing serious side effects.

Especially tell your doctor if you take:

- other medicines for high blood pressure or a heart problem
- water pills (diuretics)
- potassium supplements
- a salt substitute

Know the medicines you take. Keep a list of your medicines and show it to your doctor or pharmacist when you get a new medicine. Talk to your doctor or pharmacist before you start taking any new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

How should I take EXFORGE?

- Take EXFORGE exactly as your doctor tells you.
- Take EXFORGE once each day.
- EXFORGE can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Just take the next dose at your regular time.
- If you take too much EXFORGE, call your doctor or Poison Control Center, or go to the emergency room.
    - ~~Tell all your doctors or dentist you are taking EXFORGE if you: are going to have surgery~~
- Tell all your doctors or dentist you are taking EXFORGE if you:
    - are going to have surgery
    - go for kidney dialysis

What should I avoid while taking Exforge?

You should not take Exforge during pregnancy. See "What is the most important information I should know about Exforge."

What are the possible side effects of EXFORGE?

EXFORGE may cause **serious side effects** including:

- **harm to an unborn baby causing injury and even death.** See "What is the most important information I should know about EXFORGE?"
- **low blood pressure (hypotension)**. Low blood pressure is most likely to happen if you:
    - take water pills
    - are on a low salt diet
    - get dialysis treatments
    - have heart problems
    - get sick with vomiting or diarrhea
    - drink alcohol

Lie down if you feel faint or dizzy. Call your doctor right away.

- **more heart attacks and chest pain (angina)** in people that already have severe heart problems. This may happen when you start EXFORGE or when there is an increase in your dose of EXFORGE. Get emergency help if you get worse chest pain or chest pain that does not go away.
- **kidney problems.** Kidney problems may become worse in people that already have kidney disease. Some people will have changes in blood tests for kidney function and may need a lower dose of EXFORGE. Call your doctor if you have swelling in your feet, ankles, or hands or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing EXFORGE.
- **laboratory blood test changes in people with congestive heart failure**. Some people with congestive heart failure who take valsartan, one of the medicines in EXFORGE, have changes in blood tests including increased potassium and decreased kidney function.

The most common side effects of EXFORGE include:

- swelling (edema) of the hands, ankles, or feet.
- nasal congestion, sore throat and discomfort when swallowing
- upper respiratory tract infection (head or chest cold)
- dizziness

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of EXFORGE. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EXFORGE?

- Store EXFORGE at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep EXFORGE dry (protect it from moisture).

Keep EXFORGE and all medicines out of the reach of children.

General Information about EXFORGE

Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Do not use EXFORGE for a condition for which it was not prescribed. Do not give EXFORGE to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about EXFORGE. If you would like more information about EXFORGE, talk with your doctor. You can ask your doctor or pharmacist for information about EXFORGE that is written

for health professionals. For more information go to www.EXFORGE.com or call 1-888-839-3674.

What are the ingredients in EXFORGE?

Active ingredients: Amlodipine besylate and valsartan

The inactive ingredients of all strengths of the tablets are colloidal silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose. Additionally, the 5/320 mg and 10/320 mg strengths contain iron oxide yellow and sodium starch glycolate. The film coating contains hypromellose, iron oxides, polyethylene glycol, talc and titanium dioxide.

What is high blood pressure (hypertension)?

Blood pressure is the force of blood in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. EXFORGE can help your blood vessels relax so your blood pressure is lower. Medicines that lower blood pressure lower your chance of having a stroke or heart attack.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure and vision problems.

Revised July 2008

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Norman Stockbridge

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

SUMMARY REVIEW

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 20-990 (amlodipine/valsartan; Exforge

Sponsor: Novartis

Review date: 16 July 2008

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 21-990
DCaRP/Nguyen

Supplement 003 (submitted 24 September 2007) seeks an initial therapy claim for the combination for amlodipine and valsartan for the treatment of hypertension. The sponsor based its analyses on a full factorial study reviewed as part of the initial approval of the NDA.

There are no CMC changes and no reviews for pharmacology, toxicology, or clinical pharmacology.

There is a joint medical-statistical review by Drs. Moreschi and Liu (30 June 2008) of two studies other than the main factorial study. These studies were, I believe, provided by the sponsor for complete disclosure, but I agree with the reviewers that these studies do not contribute significantly to the matter at hand. Neither study contains a placebo group. Both studies have a higher lower bound to the inclusion criteria and show markedly different patterns of what must represent regression to the mean than does the main factorial trial, so they cannot reasonably be used to supplement the high end of the curves being added to the label to show likelihood of achieving goals from a given baseline blood pressure.

The analyses of goal-by-baseline-BP that are being added to the label have been reviewed by the statistician, and they have been the result of several iterative steps with multiple interactions with the sponsor. This activity is undocumented, but I am confident in the process that led to the labeling being approved.

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/s/

Norman Stockbridge
7/16/2008 09:27:24 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

MEDICAL REVIEW(S)

Safety Update

Since approval of Exforge in June 2007, there have been no new unexpected adverse reactions.

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/s/

Gail Moreschi
7/15/2008 11:23:40 AM
MEDICAL OFFICER

CLINICAL and STATISTICAL REVIEW

Application Type	NDA 21-990
Submission Number	S-003
Submission Code	
Letter Date	September 24, 2007
Stamp Date	
PDUFA Goal Date	July 24, 2008
Reviewers Names	Gail Moreschi, MD, MPH Ququan Liu, MD, MS
Review Completion Date	June 30, 2008
Established Name	amlodipine besylate & valsartan
Trade Name	Exforge
Therapeutic Class	Dihydropyridine CCB/ARB
Applicant	Novartis
Priority Designation	S
Formulation	Combination tablets
Dosing Regimen	Once daily
Indication	Hypertension
Intended Population	Adults

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1 EXECUTIVE SUMMARY

This sNDA was first submitted as a change in the original label from treating patients for hypertension who did not reach control with either valsartan or amlodipine alone to treatment as initial therapy for hypertension. Two additional studies for Stage II hypertension were also submitted which are reviewed here. These studies are limited for several reasons which include the fact that Exforge is compared only to amlodipine, the primary endpoint is the reduction of the systolic blood pressure not the diastolic, and ultimately hydrochlorothiazide was added to patients who did not reach goal. Also, the placebo effect was not subtracted. Therefore, these reviewers believe that the label should include Exforge as initial treatment for hypertension but that these additional studies are only approvable.

1.1 Recommendation on Regulatory Action

Approvable

1.2 Recommendation on Postmarketing Actions

NA

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This sNDA is primarily label change seeking initial treatment for hypertension. The Sponsor has also submitted two studies from the ongoing development program.

1.3.2 Efficacy

The two studies reviewed here were in patients with Stage II hypertension, not severe hypertension. The systolic blood pressure was the primary index followed. In some patients HCTZ was added in order to control the blood pressure.

1.3.3 Safety

In this submission there are no new safety findings. However, it is interesting that peripheral edema occurred more often with valsartan/amlodipine combination than with amlodipine alone.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Valsartan has been marketed as monotherapy for hypertension since 1996 in doses up to 320 mg. Amlodipine is administered as monotherapy in doses up to 10 mg. Since approval as combination therapy in June 2007, there have been no new unexpected adverse reactions.

2.2 Currently Available Treatment for Indication

Avalide (irbsarten/HCTZ; NDA 20-758/S-037) has been approved as initial therapy for hypertension.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Please refer to original NDA 21-990

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor submitted the updated label and two additional studies from their ongoing developmental program.

4.2 Table of Clinical Studies

Ref.	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
report: Doc. **listings:** Doc.	**protocol:** VAA489A2402 **invest.:** Flack J **countries:** Columbia, Ecuador, South Africa, US **start:** 8 June 2006 **end:** 16 Apr 2007 **publ.:** None	**design, goal & population:** A 12-week DB, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered val/aml combination based therapy versus aml monotherapy in Black patients with stage II hypertension. Patients whose BP is not at target (≥130 mmHg MSSBP) after 8 weeks of DB treatment can have HCTZ added. **evaluations:** Primary: Change from baseline in MSSBP. Secondary: Change from baseline in MSDBP, BP control rate (MSSBP < 140 mmHg and MSDBP < 90 mmHg). Safety: AEs/SAEs, PE, vital signs, lab values, urinalysis, ECG, pregnancy test	**total:** 572 randomized, 497 complete, 75 discontinued **age:** ≥ 18; mean age = 53.2 yrs (228 male, 344 female) **groups:** 2 (patients are to be randomized in equal numbers)	**form:** capsule + tablet **route:** p.o. **regimen:** o.d. **duration:** 1-3 to 7 day screening/ washout 12 week DB treatment **doses:** Val/Aml 160/5 mg (2 wks) then force titration to 160/10 mg (2 wks) then optional titration to 320/10 mg (4 wks) then optional addition of HCTZ 12.5 mg (4 wks). Aml 5 mg (2 wks) then force titration to Aml 10 mg (2 wks) then optional sham titration to Aml 10 mg (4 wks) then optional addition of HCTZ 12.5 mg (4 wks)	**status:** Completed **report:** Published **general results:** The Valsartan/Amlodipine combination treatment regimen produced a statistically significantly greater reduction in MSSBP from baseline compared to Amlodipine monotherapy at Week 8 (33.3 mmHg for Valsartan/Amlodipine; 26.6 mmHg for Amlodipine (p<0.05).

Ref.	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
report: Doc. **listings:** Doc.	**protocol:** VAA489A2403 **invest.:** Destro M **countries:** Belgium, Denmark, Italy, Mexico, Poland, Spain, US **start:** 9 Jun 2006 **end:** 10 Apr 2007 **publ.:** None	**design, goal & population:** An 8 - week DB, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered val/aml combination based therapy versus aml monotherapy in patients with stage II hypertension. Patients whose BP is not at target (≥130 mmHg) after 4 weeks of DB treatment can have HCTZ added. **evaluations:** Primary: Change from baseline in MSSBP. Secondary: Change from baseline in MSDBP, BP control rates. ABPM Substudy. Safety: AEs/SAEs, PE, vital signs, lab values, urinalysis, ECG, pregnancy test	**total:** 646 randomized, 577 complete, 69 discontinued (528 w, 33b, 37 a, 48 o) **age:** ≥ 18; mean age = 58.1 yrs; (324 male, 322 female) **groups:** 2 (patients are to be randomized in equal numbers)	**form:** capsule + tablet **route:** p.o. **regimen:** o.d. **duration:** 1-3 to 7 day screening/ washout 8 week DB treatment **doses:** Val/Aml 160/5 mg (2 wks) then force titration to 160/10 mg (2 wks) then optional addition of HCTZ 12.5 mg (4 wks). Aml 5 mg (2 wks) then force titration to Aml 10 mg (2 wks) then optional addition of HCTZ 12.5 mg (4 wks).	**status:** Completed **report:** Published **general results:** Patients who received Valsartan/Amlodipine exhibited a significantly greater LSM reduction from baseline in MSSBP at Week 4 (LOCF) than did those who received Amlodipine (30.1 mmHg and 23.5 mmHg, respectively; p<0.05).

4.3 Review Strategy

This was a joint review shared between the statistical and medical reviewers.

4.4 Data Quality and Integrity

A DSI inspection was not warranted.

4.5 Compliance with Good Clinical Practices

The studies were performed in accordance with standard operating procedures of the Sponsor. They were designed to ensure adherence to GCP and to ensure the protection of the patients.

4.6 Financial Disclosures

There were no unusual finical disclosures determined.

5 CLINICAL PHARMACOLOGY

Please refer to original NDA 21-990

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Two studies (CVAA489A 2402 and CVAA489A 2403) were submitted with an updated label seeking initial treatment for hypertension. These studies will be presented separately as the populations studied were different.

6.1.1 Methods

Both Studies A2402 and A2403 were double-blind, randomized, multicenter, parallel group studies evaluating the safety and efficacy of orally administered valsartan/amlodipine combination based therapy versus amlodipine in patients with Stage II hypertension. Study A2402 was completed in Black patients.

6.1.2 General Discussion of Endpoints

The endpoint was that the combination of valsartan/amlodipine produces a superior reduction in the mean sitting systolic blood pressure (MSSBP) from baseline compared to amlodipine.

6.1.3 Study Design

6.1.3.1. Study CVAA489A 2402

Title: A 12-week double-blind, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered valsartan/amlodipine combination based therapy versus amlodipine monotherapy in Black patients with stage II hypertension

Study dates: June 8, 2006 to April 16, 2007

Phase IIIb

Study Centers: A total of 74 centers in 4 countries enrolled at least one patient including Colombia (66), Ecuador (35), South Africa (161), US (773).

Primary Objective:
The primary objective was to demonstrate the superior efficacy of the combination of valsartan/amlodipine 160/10 mg and 320/10 mg treatment regimen in Black patients with stage II hypertension, by testing the hypothesis that the valsartan/amlodipine combination treatment regimen produces a superior reduction in mean sitting systolic blood pressure (MSSBP) from baseline compared to amlodipine monotherapy at Week 8.

Secondary objectives:
1. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline MSSBP after 2, 4 and 12 weeks of treatment.
2. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline mean sitting diastolic blood pressure (MSDBP) after 2, 4, 8 and 12 weeks of treatment.
3. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP < 140 mmHg and MSDBP < 90mmHg) after 12 weeks of treatment.
4. To evaluate the safety and tolerability of the valsartan/amlodipine and amlodipine treatment

regimens.

Exploratory objectives:
1. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching diastolic control (defined as MSDBP <90 mmHg) after 2, 4, 8 and 12 weeks of treatment.
2. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP < 140 mmHg and MSDBP < 90mmHg) after 2, 4 and 8 weeks of treatment.
3. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the incidence and severity of edema.

Study Design:
This was a randomized, double-blind, multinational, two arm, parallel group study. At Visit 2 (Day 1), eligible patients were randomized in a 1:1 ratio to receive valsartan/amlodipine 160/5 mg or amlodipine 5 mg for 2 weeks. At Visit 3 (Week 2), all patients were force titrated to receive an additional 5 mg of amlodipine for 2 weeks. From Visit 3 onwards, patients were treated until the end of the study (Visit 6, Week 12) with either valsartan/amlodipine 160/10 mg or amlodipine 10 mg, unless further optional upward titration was needed.

At Visit 4 (Week 4), patients treated with valsartan/amlodipine 160/10 mg who had not reached the target systolic blood pressure (MSSBP ≥ 130 mmHg) could be up titrated at the investigator's discretion to receive valsartan/amlodipine 320/10 mg, while patients treated with amlodipine 10 mg who had not reached the target systolic blood pressure continued at their current dose (additional placebo to match valsartan 160 mg was administered). At Visit 5 (Week 8), patients in either treatment regimen who had not reached target for systolic blood pressure (<130 mmHg) HCTZ 12.5 mg could be added open label at the discretion of the investigator.

Figure 1 Study Design

Screening/Washout	**Double-blind treatment**				
(1 week)	(12 weeks)				
Visit 1	**2**	**3**	**4**	**5**	**6**
Days -7 to -3	Day 1	Week 2	Week 4	Week 8	Week 12
	↓ Randomization				
				+HCTZ 12.5 mg**	
			+valsartan/amlodipine 320/10 mg**		
		valsartan/amlodipine 160/10 mg*			
	valsartan/amlodipine 160/5 mg				
	amlodipine 5 mg				
		amlodipine 10 mg*			
			+placebo**		
				+HCTZ 12.5 mg**	

* Forced titration
** Optional titration (MSSBP ≥ 130 mmHg)

Main criteria for inclusion:
The study population consisted of Black male and female hypertensive outpatients ≥ 18 years of age with stage II hypertension (MSSBP ≥ 160 mmHg and <200 mmHg).

Table 1 Summary of Eligibility based on medications and Blood Pressure

	Number of Antihypertensive Drugs Being Taken at Visit 1			
BP at Visit 1 MSSBP	0 or 1	2	3	> 3
<140 mmHg	Yes	Yes	Yes	No
≥ 140 and <180 mmHg	Yes	Yes	No	No
≥ 180 mmHg	Yes	No	No	No

Once eligibility was determined, patients entered a 3 to 7 day wash-out period. Patients were instructed to take study medication every morning except on the morning of scheduled study Visits 3, 4, 5 and 6 when study medication was taken at the investigational site after office blood pressure measurements were obtained.

The treatment regimens selected in this study design, 160 mg valsartan / 5 mg amlodipine in combination with a forced titration to 160 mg valsartan / 10 mg amlodipine and later to 320 mg valsartan/10 mg amlodipine (if needed) were chosen.

Table 2 Dosing scheme

Treatment Arm	Visit 2	Visit 3	Visits 4 & 5 MSSBP < 130 mmHg	Visits 4 & 5 MSSBP ≥ 130 mmHg
Val/aml treatment regimen	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg valsartan 160 mg amlodipine 5 mg amlodipine 5 mg HCTZ 12.5 mg*
Amlodipine treatment regimen	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg placebo valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg HCTZ 12.5 mg*

For both treatment arms the daily dose consisted of one capsule, by mouth, at approximately 8:00 AM from each of 3 or 4 bottles (depending on MSSBP value) containing double blind investigational medication.
* At Visit 5, patients in both treatment arms whose MSSBP was not at systolic target (MSSBP < 130 mmHg) could receive a supplementary dose of open label HCTZ 12.5mg at the investigator's discretion.

Treatment Duration:
The double-blind study medication given to the enrolled patients consisted of valsartan 160 mg capsules (and matching placebo) and amlodipine 5 mg capsules (and matching placebo) for oral administration. Patients who were electively up-titrated to 12.5 mg HCTZ received individual open-label bottles at Visit 5. The duration of the study, including all phases, was 13 weeks. The duration of double-blind treatment was 12 weeks.

Efficacy and safety measurements assessed:
Full details of the assessments are described in the table below.

Table 3 Visit Schedule

Visit	1	2[3]	3	4	5	6
Week	-1 (Day -7/-3)	0 (Day 1)	2	4	8	12
Written informed consent	X					
Demography	X					
Medical history	X					
Inclusion/exclusion criteria	X	X				
Prior/Concomitant medications	X	X	X	X	X	X
Randomization		X				
Dispense home BP measuring device	X					
Dispense study medication		X	X	X	X	
Drug accountability			X	X	X	X
Vital signs and BP measurement	X	X	X	X	X	X
Weight and Height[4]	X					X
Adverse events		X	X	X	X	X
Serious adverse events		X	X	X	X	X
Physical examination	X					
Interim physical examination		X	X	X	X	X
ECG	X					
Hematology	X					X
Blood chemistry	X				X[1]	X
Urinalysis	X					X
Serum Pregnancy test	X					X
Study Completion form[2]						X

1 At visit 5 only Potassium, BUN and creatinine were measured
2 Or at study discontinuation
3 For those patients whose MSSBP was < 160 mmHg after 3 days wash out period, Visit 2 was rescheduled after an additional 4 day washout
4 Height was measured at Visit 1 only

Concomitant medications which were not permitted:
• Drugs approved for the treatment of hypertension even if prescribed for another indication. (Beta-blocker ophthalmic preparations are permitted.)
• Any antidepressant drugs in the MAO inhibitor class, tricyclics and venlafaxine hydrochloride (Effexor®). Other psychotropic drugs such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) were allowed if well tolerated when previously taken and the patient had been on a stable dose for the previous 3 months.
• Chronic use of oral anti-inflammatory steroidal drugs was prohibited. Topical and inhaled steroids and non-steroidal anti-inflammatory drugs (NSAIDS) were allowed. The long-term chronic use of aspirin for pain or cardiac prophylaxis was allowed, provided the total daily dose did not exceed 325 mg. Acetaminophen for chronic or acute pain was allowed.
• Hormonal contraceptives beginning 4 weeks prior to randomization and continuing in trial.
• Thyroid medication and/or estrogen replacement therapy, unless these had been stable maintenance replacement doses for the 6 months preceding Visit 1.
• Chronic administration (defined as > 3 days per week) of sympathomimetic drugs such as those found in nasal decongestants, oral decongestants, diet aids and bronchodilators.
• Antacids in an amount greater than the package labeling.
• Ergot and serotonin (5-hydroxytryptamine) receptor agonist preparations.
• Tamsulosin hydrochloride (Flomax®).
• Sildenafil (Viagra®) and vardenafil (Levitra®) were disallowed within 24 hours prior to any scheduled visit. Tadalafil (Cialis®) was disallowed within 48 hours prior to any scheduled visit.
• Antiarrhythmic drugs, including digoxin.

• Diuretics of any kind (other than study medication).
• Maintenance doses of nitrates were allowed, but if taken 24 hours before visit, visit was rescheduled
• Lithium.
• Opioids and barbiturates.
• Adrenocorticotropic hormone (ACTH).
• Cholestyramine and colestipol resins.
• Oral anticoagulants including warfarin and heparin.
• Drugs approved for the treatment of adult ADHD including Ritalin®, Focalin®, Adderall®, Strattera®, and Concerta®.
• Potent inhibitors of cytochrome P450 3A4 (CYP3A4) including itraconazole, ketoconazole, clarithromycin, erythromycin, nefazodone, and HIV protease inhibitors.

All other non-study medications were allowed provided the need for such medication(s) represented a continuation of a need that existed prior to study entry and remained at stable doses throughout the length of the study. If clinically indicated, a dosage adjustment on a concomitant medication could be made.

Efficacy:
The primary efficacy variable was change from baseline in MSSBP (mmHg) at Week 8 (or LOCF).

Secondary efficacy variables:
Change from baseline MSDBP at Week 8 (or LOCF).
Change from baseline MSSBP and MSDBP at Weeks 2, 4 and 8 and 12.
Overall BP control after 12 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg).

Exploratory efficacy variables:
Overall BP control rate at Weeks 2, 4 and 8 (MSSBP < 140 mmHg and MSDBP < 90 mmHg).
Diastolic BP control rate at Weeks 2, 4, 8 and 12 (MSDBP < 90 mmHg).
Unadjusted systolic BP target rate, systolic BP control rate, diastolic BP control rate and overall BP control rate.

Safety:
Safety assessments consisted of all adverse events (AE) and serious adverse events (SAE), the regular monitoring of hematology and blood chemistry, regular measurement of vital signs, weight and the performance of physical examinations and pregnancy testing. An ECG evaluation and height were conducted at Visit 1.

Statistical methods:
Primary: The primary efficacy variable was analyzed using analysis of covariance (ANCOVA). Treatment, country, length of washout received were fitted as factors in the model and baseline MSSBP as a covariate. The change from baseline LSM, the difference between LS means, (valsartan/amlodipine vs. amlodipine) and two-sided 95% confidence interval were presented.

The null hypothesis would be rejected if the 2-sided p-value < 0.05. For patients who discontinued prior to week 8, the last post-baseline MSSBP measurement collected was carried forward (LOCF). Analysis was performed using the Intent-to-Treat (ITT) population. The primary analysis was repeated using the Per-Protocol population.

Secondary: The change from baseline in MSDBP at Week 8 (or LOCF) and the change from baseline in MSSBP and MSDBP at Visits 3, 4, 5 and 6 (weeks 2, 4, 8 and 12 respectively) was analyzed using the same model as described for the primary analysis.

Patients reaching overall BP control in each treatment regimen at endpoint Visit 6 (week 12) were analyzed using a logistic regression model with treatment and length of washout as fixed factors and baseline MSSBP and baseline MSDBP as covariates. The point estimate for the odds ratio (valsartan/amlodipine vs. amlodipine) and two-sided 95% confidence interval around the odds ratio was presented.

Protocol Amendment and Deviations:
The purpose of Amendment 1 (July 26, 2006), was to clarify for consistency the upper limits of systolic and diastolic blood pressure criteria and the target systolic blood pressure criteria for optional upward titration throughout the protocol, add additional excluded concomitant medications for the treatment of adult ADHD and potent inhibitors of cytochrome P450 3A4 (CYP3A4), and clarify exclusion criteria number 3 which defines the end of the down titration period for those patients who need to taper off of prior antihypertensive medication.

The most frequently reported major deviations were time of BP measurement < 20 or > 30 hours after the last dose of study medication (12.2% for valsartan/amlodipine; 14.7% for amlodipine), study drug interruption > 3 consecutive days prior to Visit 6 (4.2% for valsartan/amlodipine; 5.2% for amlodipine), and MSSBP < 160mmHg or ≥ 200 at Visit 2 (4.2% for valsartan/amlodipine; 3.5% for amlodipine).

No interim analysis was performed.

6.1.3.2 Study CVAA489A 2403

Only important differences from the above study A2402 will be presented here.

Title: An 8-week double-blind, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered valsartan / amlodipine combination based therapy versus amlodipine monotherapy in patients with stage II hypertension

Phase IIIB

Dates: June 9, 2006 to April 10, 2007

Study center(s): A total of 75 centers in 6 countries enrolled at least one patient including US (189), Italy (118), and Mexico

Objectives:
The primary objective was to demonstrate the superior efficacy of the combination of valsartan/amlodipine 160/10 mg in patients with stage II hypertension, by testing the hypothesis that the valsartan/amlodipine 160/10 mg combination regimen produces a superior reduction in MSSBP from baseline compared to amlodipine 10 mg monotherapy at week 4.

Secondary objectives:
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline MSSBP after 2 and 8 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline MSDBP after 2, 4 and 8 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP <140 mmHg and MSDBP <90mmHg) after 8 weeks of treatment.
• To evaluate the safety and tolerability of the valsartan/amlodipine and amlodipine treatment regimens.

Exploratory objectives:
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching diastolic control (defined as MSDBP <90 mmHg) after 2, 4 and 8 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP <140 mmHg and MSDBP <90mmHg) after 2 and 4 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the incidence and severity of edema.
• To explore the effect of the valsartan/amlodipine and amlodipine treatment regimens on the 24 hour Ambulatory Blood Pressure Monitoring (ABPM) profiles after 4 weeks of treatment.
• To evaluate mean systolic and diastolic ambulatory blood pressure over 24 hours at week 4
• To evaluate nocturnal and diurnal systolic and diastolic load at week 4
• To explore the effect of the valsartan/amlodipine and amlodipine treatment regimens on non-dipper pattern, where non-dipper is defined as <10 % decline in night-time mean versus the day-time mean of systolic ABPM

Study Design:
This was a randomized, double-blind, multinational, two arm, parallel group study. This study was designed to demonstrate a difference of 3.7 mmHg between treatment arms. The study population consisted of male and female adult outpatients with a documented diagnosis of stage II hypertension, defined as MSSBP of ≥ 160 mmHg and < 200 mmHg. At Visit 2 (day 1), eligible patients were randomized in a 1:1 ratio to receive valsartan/amlodipine 160/5 mg or amlodipine 5 mg for 2 weeks. At Visit 3, all patients were force titrated to receive an additional 5 mg of amlodipine for 2 weeks. From Visit 3 onwards, patients were treated until the end of the study (Visit 5, week 8) with either valsartan/amlodipine 160/10 mg or amlodipine 10 mg, unless the addition of HCTZ was needed to achieve a target MSSBP < 130 mmHg.

Figure 2 Study design

Screening/Washout	Double Blind Treatment			
1- week	8-weeks			
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Day -7 to Day -3	Day 1	Week 2	Week 4	Week 8
	↓ Randomization			
			**+ HCTZ 12.5 mg	
		*valsartan 160 mg / amlodipine 10 mg		
	valsartan 160 mg / amlodipine 5 mg			
	amlodipine 5 mg			
		*amlodipine 10 mg		
			**+ HCTZ 12.5 mg	

* Forced titration
** Optional titration (MSSBP ≥ 130 mmHg

Main criteria for inclusion:
The study population consisted of male and female hypertensive outpatients ≥ 18 years of age with stage II hypertension (MSSBP ≥ 160 mmHg and < 200 mmHg). Patients with a systolic blood pressure ≥ 200 mmHg and/or a diastolic blood pressure ≥ 120 mmHg did not meet inclusion criteria.

Table 4 Summary of eligibility

	Number of Antihypertensive Drugs Being Taken at Visit 1			
BP at Visit 1 MSSBP	0 or 1	2	3	> 3
< 140 mmHg	Yes	Yes	Yes	No
≥ 140 and < 180 mmHg	Yes	Yes	No	No
≥ 180 mmHg	Yes	No	No	No

Once eligibility was determined, laboratory samples were collected for evaluation, and patients taking antihypertensive medication entered a 3 to 7 day washout period.

Duration of treatment:
The duration of the study, including all phases, was 9 weeks. The duration of double-blind treatment was 8 weeks.

Treatments:
At Visit 1 (screening), patients meeting eligibility criteria were directed to discontinue their antihypertensive medication for a 3 to 7 day washout period. At Visit 2, eligible patients were assigned to either combination therapy with valsartan/amlodipine 160/5 mg or amlodipine 5 mg monotherapy in a ratio of 1:1. Patients in both groups took 3 capsules/day for 2 weeks (valsartan 160 mg + amlodipine 5 mg + placebo matching amlodipine 5 mg OR amlodipine 5 mg plus 2 placebo capsules to match amlodipine and valsartan).

At Visit 3, all patients were force titrated to receive an additional 5 mg of amlodipine for 2 weeks. From this point forward, patients were treated until the end of the study (Visit 5, week 8) with either valsartan/amlodipine 160/10 mg or amlodipine 10 mg. At Visit 4, if the patient had not reached target systolic blood pressure (MSSBP < 130 mmHg), 12.5 mg HCTZ open label

medication could be added to the previous treatment regimen at the discretion of the investigator. HCTZ was not to be added if the patient had reached target systolic blood pressure.

Table 5 Dosing scheme

Treatment Arm	Visit 2	Visits 3 & 4
valsartan/amlodipine treatment regimen	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg
amlodipine treatment regimen	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg
For both treatment arms the daily dose consisted of one capsule, by mouth, at approximately 8:00 AM from each of 3 bottles containing double blind investigational medication. Patients who received open label HCTZ took 4 capsules/day (3 capsules double-blind + one capsule open label).		

Efficacy and Safety Assessment Schedule:

Table 6 Assessment schedule

Visit	1	2[4]	3	4	5
Week	-1 (day -7/-3)	0 (day 1)	2	4	8
Written informed consent	X				
Demography	X				
Medical history	X				
Inclusion/exclusion criteria	X	X			
Prior/Concomitant medications	X	X	X	X	X
Randomization		X			
Dispense home BP measuring device	X				
Dispense study medication[5]		X	X	X	
Drug accountability			X	X	X
Vital signs and BP measurement	X	X	X	X	X
ABPM[1]		X		X	
Adverse events		X	X	X	X
Serious adverse events		X	X	X	X
Physical examination	X				
Interim physical examination		X	X	X	X
ECG	X				
Hematology	X				X
Blood chemistry	X			X[2]	X
Serum Pregnancy test	X				X
Study Completion Form[3]					X

[1] For ABPM sub-study participants only (approx. 100 patients in selected centers)
[2] Only potassium, BUN and creatinine were measured at Visit 4
[3] Or at study discontinuation
[4] For patients with MSSBP < 160 mmHg after 3 day washout period Visit 2 was rescheduled after an additional 4 day washout
[5] ABPM sub-study patients were dispensed study medication according to Table 9-5

Table 7 24-hour ABPM Schedule

Visit	2	24-hours after V2	4	24-hours after V4
Week	Day 1		4	
Perform visit assessments	X		X	
Record BP and pulse before application of ABPM device	X		X	
Apply ABPM device	X		X	
Perform correlation	X		X	
Verify success criteria		X		X
Remove ABPM		X		X
Dispense study medication		X	X	X[1]
1 – HCTZ, if indicated, was dispensed 24 hours after V4.				

Office blood pressure measurements were made using an Omron blood pressure monitor in accordance with the Guidelines for Management of Hypertension, British Hypertension Society 2004, at trough (24 hours ± 3 hours post-dose), i.e. just prior to taking the morning dose of medication. The same arm was used at all visits. Ideally, the same clinician obtained blood pressure measurements for the same patients at each visit, using the same equipment.

Sitting and standing blood pressure were measured at each visit. After the patient had been sitting for 5 minutes, blood pressure was measured three times at 2 to 3 minute intervals. The mean of the three sitting blood pressure measurements was used as the average of sitting office blood pressure at each visit. Standing BP was measured only once, within 2 minutes after the last sitting BP measurement.

Self measured blood pressure (SMBP) was included in the study design to aid patients and investigators in identifying potentially emergent hypertensive situations that may have occurred during prior antihypertensive washout and throughout the course of the trial. SMBP information was not recorded for analysis.

Ambulatory Blood Pressure Monitoring (ABPM) was conducted over a 24-hour period at two time points during the study, V2 and V4. Following office blood pressure measurements, the ABPM device was applied. The device was pre-set to collect readings every 15 minutes during the day (6AM to 10PM) and every 30 minutes during the night (10PM to 6AM). Patients were asked to return to the site the following day (25-26 hours after the start of ABPM) to remove the ABPM device. At Visit 2 patients in the ABPM sub-study received their first dose of double-blind medication upon removal of the ABPM device, 25-26 hours after Visit 2. Mean hourly systolic and diastolic blood pressure were calculated for each patient at post dosing hours 1-24. Each patient's post-dosing hours (1-24) was determined relative to that patient's dosing time. Only valid ABPM measurements made at or within 24 hours of the dosing time were used in this calculation.

All available values at a certain "post-dosing" hour were weighted equally to obtain the mean systolic and diastolic values for that "post-dosing" hour. The mean systolic and diastolic ambulatory blood pressure over 24 hours for a patient were calculated by averaging the patient's available hourly means (assigning equal weight to the available hourly means) for post dosing hours 1-24. All other evaluation of ABPM was done centrally and instructions for transmitting the data were provided. ABPM readings remained blinded to patients, investigators and study site personnel.

Efficacy:
The primary efficacy variable was the change from baseline in mean sitting systolic blood pressure (MSSBP) LOCF Week 4. LOCF Week 4 was defined as the week 4 value or last non-missing post-dose value (last observation carried forward). The parameter was in the protocol named as Endpoint (Week 4).

Secondary efficacy variables:

Change from baseline MSDBP at Week 4 (last observation carried forward; LOCF)
Change from baseline MSSBP and MSDBP at Weeks 2, 4 and 8
Overall BP control rate after 8 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg)

Exploratory efficacy variables:
Overall BP control rate at Weeks 2 and 4 (MSSBP < 140 mmHg and MSDBP < 90 mmHg)
Diastolic BP control rate at Weeks 2, 4 and 8 (MSDBP < 90 mmHg)
Unadjusted systolic BP target rate, systolic BP control rate, diastolic BP control rate and overall BP control rate

Safety:
Safety assessments consisted of all adverse events (AE) and serious adverse events (SAE), hematology and blood chemistry, measurement of vital signs and the performance of physical examinations and pregnancy testing. An ECG evaluation was conducted at Visit 1.

Statistical methods:
The primary efficacy variable was the change from baseline in MSSBP (mmHg) at LOCF Week 4. The change from baseline in MSSBP LOCF Week 4 was analyzed using analysis of covariance (ANCOVA). Treatment, country and length of washout were fitted as factors and baseline MSSBP as a covariate. The least square means, treatment difference with 95% confidence interval, and p-value were presented.

The primary and secondary analyses were performed using the ITT population. The secondary variables, change from baseline MSSBP and MSDBP were analyzed separately for weeks 2, 4, week 4 LOCF (MSDBP only) and 8 with the same model as described for MSSBP in the primary analysis. In addition, MSSBP and MSDBP were summarized using descriptive statistics by treatment strategy and time point (Week 2, Week 4, pre-HCTZ LOCF Week 4 and Week 8). Subgroup analysis for severity of hypertension at baseline, diabetic status, age group, sex and race were performed.

The number of patients with overall BP control (MSSBP < 140 mmHg and MSDBP < 90 mmHg) at Week 8 was analyzed using a logistic regression model with treatment and length of wash-out as fixed factors, baseline MSSBP and baseline MSDBP as covariates.

The change from baseline in mean ambulatory blood pressure monitoring (ABPM) over 24 hours (systolic and diastolic), the change from baseline in daytime/nighttime (systolic and diastolic) was analyzed using an ANCOVA model with treatment, country, length of wash-out as factors and baseline variable as a covariate. To estimate hourly changes from baseline to assess intra-dosing effects, a repeated-measures ANCOVA with treatment, country, length of wash-out, post-dosing hours (hour 0,1, 2, 3, …, or 23) as factors and baseline mean 24-hour MASBP as a covariate was applied. Treatment by post-dosing-hour interaction was included in the model. All analyses for ABPM were carried out using the ABPM population.

Summary statistics for systolic diurnal load (the proportion of SBP readings >135 mmHg), the diastolic diurnal load (the proportion of DBP readings >85 mmHg), the systolic nocturnal load (the proportion of SBP readings >120 mmHg) and the diastolic nocturnal load (the proportion of DBP readings >70 mmHg) were presented by visit and treatment group. Summary statistics for Smoothness Index by each treatment group was calculated.

The rate of patients experiencing edema was compared using logistic regression with treatment, sex, race and age category (<65, ≥ 65 yrs) as factors. The same analysis was repeated for peripheral edema.

Protocol Amendment and Deviations:
The purpose of Amendment 1 (July 14, 2006), was to clarify for consistency the upper limits of systolic and diastolic blood pressure criteria throughout the protocol, add additional excluded concomitant medications for the treatment of adult ADHD and potent inhibitors of cytochrome P450 3A4 (CYP3A4), and clarify exclusion criteria number 3 which defined the end of the down-titration period for those patients who needed to taper off of prior antihypertensive medication.

Table 8 Patient disposition - Randomized population

Disposition Reason	Val/Aml N=322 n (%)	Amlodipine N=324 n (%)	Total N=646 n (%)
Completed	289 (89.8)	288 (88.9)	577 (89.3)
Discontinuations	33 (10.2)	36 (11.1)	69 (10.7)
Adverse event(s)	19 (5.9)	19 (5.9)	38 (5.9)
Subject withdrew consent	7 (2.2)	15 (4.6)	22 (3.4)
Lost to follow-up	3 (0.9)	1 (0.3)	4 (0.6)
Administrative problems	1 (0.3)	1 (0.3)	2 (0.3)
Abnormal test procedure result(s)	2 (0.6)	0 (0.0)	2 (0.3)
Protocol deviation(s)	1 (0.3)	0 (0.0)	1 (0.2)

Protocol deviations occurred in 92 patients (28.6%) in the valsartan/amlodipine treatment strategy, and in 87 patients (26.9%) in the amlodipine treatment strategy. Approximately half were major deviations (46 /14.3% for valsartan/amlodipine; 47 / 14.5% for amlodipine). The most frequently reported major deviations were time of BP measurement < 20 hours before or > 30 hours after the last dose of study medication (23 / 7.1% for valsartan/amlodipine; 26 /8.0% for amlodipine) and patients with a visit 1 MSSBP ≥ 140 mmHg and <180 mmHg.

6.1.4 Efficacy Findings

6.1.4.1 Study CVAA489A 2402

Efficacy assessments:
The following populations were used in the analysis:
Randomized population (RAN): All patients who had received a randomization number, regardless of study medication intake. ITT population (ITT): All patients as randomized who had a baseline and at least one postbaseline efficacy assessment. Following the intent-to-treat

principle, patients were analyzed according to the treatment they were assigned to at randomization.

Safety population (SAF): All patients who received at least one dose of double-blind study drug. Patients were analyzed according to treatment received.

Per-Protocol population (PP): All ITT patients who completed the trial without any major deviations from the protocol procedures in a manner liable to affect the efficacy assessment. Protocol deviations that would exclude a patient from the per-protocol population were prespecified prior to unblinding the treatment codes for analyses. The supplemental efficacy population is the PP population. It was used to assess robustness of the primary efficacy analysis results from the ITT population.

Study Medication:
The duration (Weeks) of the randomized trial medication was summarized for the Safety population by treatment strategy. Study drug interruptions were not accounted while calculating treatment duration since they were not captured on the CRFs.

The following algorithm was used to calculate the treatment duration:
If the last date the patient took study drug was known, treatment duration was calculated as:
Treatment duration (Weeks) = (last study drug date – randomization date + 1)/7.

If the last date the patient took study drug was unknown or missing, the last visit date was substituted: Treatment duration (Weeks) = (last visit date – randomization date + 1)/7.

If the last date the patient took study drug was incomplete:
• Treatment duration (days) was determined using Novartis standard convention – when calculating relative days, partial dates with missing day only will assumed to be 15th of the month, and partial dates with both missing day and month was assumed to be July 1.
• If the imputed date is beyond the last visit date then the last visit date was used instead.
• If the imputed date is before treatment start date then last date was treatment start date+1.

Summary statistics (mean, SD, median, minimum, maximum) of the duration exposure (Weeks) to study medication, regardless of dose levels, were presented by treatment strategy. Frequency counts by following exposure categories were presented:
0 - <2 Weeks
2 - <4 Weeks
4 - <8 Weeks
8 - ≤ 12 Weeks
Actual durations of greater than 12 Weeks were included in the "8 - <=12 Weeks" category.

Frequency counts and percentages were also presented in the following four categories,
• No up titration, no HCTZ intake
• Up titration but no HCTZ intake
• No up titration but HCTZ intake

• Both up titration and HCTZ intake
for the combined HCTZ intake and the up titration of valsartan/amlodipine 320/10 mg separately for both treatment strategies.

Concomitant medications as well as significant non-drug therapies were summarized by treatment strategy for the Safety population. Concomitant medications and significant nondrug therapies were defined as any medication or significant non-drug therapies taken on or after visit 2, which also included medications and significant non-drug therapies that were ongoing at the start of Visit 2.

Due to a data programming issue, prior and concomitant medications could not be separated. This had a minor implication on the reporting of the data. Prior and concomitant medications were therefore summarized in one table.

Patients were assigned into the category of length of wash-out as follows:
• A patient with no prior antihypertensive medication recorded within the last 3 months before visit 1 was assigned to the **naïve group** (based on no entry for prior antihypertensive medication or the end date of the antihypertensive medication > 90 days in comparison to the visit 1 date).
• If the antihypertensive end date was not missing, a patient who had not stopped the antihypertensive medication more than 90 days before visit 1 was assigned to either the **3 day washout category** (actual washout of 0-4 days) or the **7 day wash-out category** (actual washout of ≥ 5 days) depending on his actual number of wash-out days. The actual number of wash-out days was calculated as Visit 2 date - End date of the antihypertensive medication -1.

• If the antihypertensive medication end date was missing, the following rules were applied:
1. If the day of month was missing, it was set to either the last day of the month or the date of Visit 1, if Visit 1 occurred earlier than the end of the month.
2. If the month was missing, the date was set to the end of the year or the date of Visit 1 if Visit 1 occurred earlier than the end of the year.

If the antihypertensive medication end date was missing and there was any indication that the patient had taken antihypertensive medication within the past 3 months prior to Visit 1, the length of wash-out was set to missing.

Severity of hypertension at baseline (Visit 2):
1. Baseline MSSBP < 180 mmHg
2. Baseline MSSBP ≥ 180 mmHg

Diabetic status (2 levels):
1. Yes = the patient has controlled type 2 diabetes mellitus
2. No = the patient does not have type 2 diabetes mellitus

Age group (2 levels):
1. age < 65
2. age ≥ 65

Patient Disposition:

Table 9 Disposition of Patients

Disposition Reason	Val/Aml N=286 n (%)	Amlodipine N=286 n (%)	Total N=572 n (%)
Screened			1042
Completed	247 (86.4)	250 (87.4)	497 (86.9)
Discontinued	39 (13.6)	36 (12.6)	75 (13.1)
Lost to follow-up	13 (4.5)	5 (1.7)	18 (3.1)
Subject withdrew consent	9 (3.1)	8 (2.8)	17 (3.0)
Adverse event(s)	7 (2.4)	9 (3.1)	16 (2.8)
Protocol deviation	8 (2.8)	7 (2.4)	15 (2.6)
Administrative problems	2 (0.7)	2 (0.7)	4 (0.7)
Abnormal test procedure result(s)	0 (0.0)	2 (0.7)	2 (0.3)
Unsatisfactory therapeutic effect	0 (0.0)	2 (0.7)	2 (0.3)
Abnormal laboratory value(s)	0 (0.0)	1 (0.3)	1 (0.2)

Demographic and Baseline Characteristics:

Table 10 Demographics by treatment strategy in Randomized population

Demographic variable	Val/Aml N=286	Amlodipine N=286	Total N=572
Age (years)			
n	286	286	572
Mean (SD)	52.9 (10.18)	53.6 (11.79)	53.2 (11.01)
Range	22-81	22-87	22-87
Age Group (years)			
< 65	244 (85.3%)	231 (80.8%)	475 (83.0%)
≥ 65	42 (14.7%)	55 (19.2%)	97 (17.0%)
< 70	265 (92.7%)	253 (88.5%)	518 (90.6%)
≥ 70	21 (7.3%)	33 (11.5%)	54 (9.4%)
< 75	279 (97.6%)	270 (94.4%)	549 (96.0%)
≥ 75	7 (2.4%)	16 (5.6%)	23 (4.0%)
Gender			
Male	120 (42.0%)	108 (37.8%)	228 (39.9%)
Female	166 (58.0%)	178 (62.2%)	344 (60.1%)
Race			
Black	286 (100%)	286 (100%)	572 (100%)
Ethnicity			
Hispanic/Latino	46 (16.1%)	49 (17.1%)	95 (16.6%)
Other	237 (82.9%)	236 (82.5%)	473 (82.7%)
Mixed Ethnicity	1 (0.3%)	0 (0.0%)	1 (0.2%)
Height (cm)			
n	286	286	572
Mean (SD)	166.7 (9.87)	167.4 (9.89)	167.0 (9.88)
Range	142-198	142-201	142-201
Weight (kg)			
n	285	284	569
Mean (SD)	89.3 (20.94)	91.1 (21.73)	90.2 (21.34)
Range	50-175	55-195	50-195
BMI (kg/m2)			
n	285	284	569
Mean (SD)	32.1 (6.66)	32.5 (7.23)	32.3 (6.95)
Range	18-55	19-73	18-73

Table 11 Baseline characteristics by treatment strategy in Randomized population

Parameter	Val/Aml N=286	Amlodipine N=286	Total N=572
MSSBP (mmHg)			
N	286	285	571
Mean (SD)	170.4 (9.62)	170.5 (8.92)	170.5 (9.27)
Range	116-199	150-198	116-199
MSDBP (mmHg)			
N	286	285	571
Mean (SD)	98.5 (10.94)	98.2 (10.14)	98.3 (10.54)
Range	69- 120	76- 129	69-129
Sitting pulse (bpm)			
N	286	285	571
Mean (SD)	76.5 (12.81)	77.7 (13.06)	77.1 (12.94)
Range	40-125	48-116	40-125
Standing SBP (mmHg)			
N	284	279	563
Mean (SD)	169.5 (15.11)	169.5 (13.76)	169.5 (14.44)
Range	106-208	113-212	106-212
Standing DBP (mmHg)			
N	284	279	563
Mean (SD)	102.1 (12.61)	102.6 (11.40)	102.3 (12.02)
Range	68-134	76-134	68-134
Standing pulse (bpm)			
N	284	279	563
Mean (SD)	80.1 (13.92)	82.5 (14.34)	81.3 (14.17)
Range	47-172	49-169	47-172
Length of washout category			
Treatment naive	51 (17.8%)	56 (19.6%)	107 (18.7%)
3 days (0-4 days)	118 (41.3%)	128 (44.8%)	246 (43.0%)
7 days (≥ 5 days)	117 (40.9%)	102 (35.7%)	219 (38.3%)
Diabetes status			
No	239 (83.6%)	245 (85.7%)	484 (84.6%)
Yes	47 (16.4%)	41 (14.3%)	88 (15.4%)
Hypertension severity at baseline			
MSSBP < 180 mmHg	247 (86.4%)	243 (85.0%)	490 (85.7%)
MSSBP ≥ 180 mmHg	39 (13.6%)	42 (14.7%)	81 (14.2%)

Primary efficacy results:
The primary efficacy variable was the change from baseline to Week 8 in MSSBP. The adjusted least square mean change was -33.3 mmHg in the valsartan/amlodipine regimen and -26.6 mmHg in the amlodipine regimen. The difference in the reduction was statistically significant ($p<0.0001$). Similar reductions were achieved in the Per Protocol population.

Table 12 Change from baseline in MSSBP (mmHg) at Week 8 (LOCF) by treatment strategy (Intent-to-treat population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=278)	277	170.5	-33.3 (1.20)	-6.6	(-9.12, -4.11)	<.0001*
Amlodipine (N=278)	278	170.6	-26.6 (1.18)			

N is the number of patients in the ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 8 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine.
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Table 13 Supportive analysis of the primary efficacy variable: Change from baseline in MSSBP at Week 8 (LOCF) by treatment strategy (Per protocol population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=211)	211	171.3	-33.7 (1.37)	-6.4	(-9.25, -3.50)	<.0001*
Amlodipine (N=205)	205	171.3	-27.3 (1.37)			

N is the number of patients in PP population; n is the number of PP patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 8 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine.
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Secondary efficacy results for MSDBP and MSSBP are not included in this review.

Reviewer's comment:
The FDA statistical reviewer also conducted a sub-group analysis by region. The result showed patients who received valsartan/amlodipine exhibited greater reduction in change from baseline in MSSBP at week 8 than did those who received amlodipine in both U.S and non-US populations.

Sub-group Analysis by Region

Region	Treatment	N	Baseline Mean	LSM Change from Baseline	Difference	95% CI
US	Val/Aml	194	170.75	-28.76	-6.06	-9.21, -2.91
	Amlodipine	193	170.40	-22.70		
Non-Us	Val/Aml	83	170.06	-36.21	-8.1	-12.20, -4.14
	Amlodipine	85	171.01	-28.05		

Exploratory analysis results:
Overall blood pressure control was defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg. At Week 8 (LOCF), there were significantly greater proportions of patients who achieved overall blood pressure control in the valsartan/amlodipine group than in the amlodipine group (48.4% vs. 29.5%). This was also true at Weeks 2, 4, 8 and 12.

Table 14 Proportion of unadjusted overall BP control by week and treatment ITT

Timepoint	Treatment	n	No. (%) of BP controlled [1]	95% CI*
Week 2	Val/Aml (N=278)	277	78 (28.2)	(22.86, 33.46)
	Amlodipine (N=278)	278	51 (18.3)	(13.80, 22.90)
Week 4	Val/Aml (N=278)	267	115 (43.1)	(37.13, 49.01)
	Amlodipine (N=278)	269	82 (30.5)	(24.98, 35.98)
Week 8	Val/Aml (N=278)	257	128 (49.8)	(43.69, 55.92)
	Amlodipine (N=278)	265	80 (30.2)	(24.66, 35.72)
Week 12	Val/Aml (N=278)	250	143 (57.2)	(51.07, 63.33)
	Amlodipine (N=278)	251	90 (35.9)	(29.92, 41.79)

Week 8^ is Week 8 or the last observation carried forward value.
N is the number of patients in ITT population; n is the number of ITT patients with a non-missing measurement at that timepoint.

[1] overall BP control defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg.
* The asymptotic confidence intervals are presented.

Systolic BP control was defined as MSSBP <140 mmHg. Compared to those who received amlodipine, larger proportions of patients who received valsartan/amlodipine achieved systolic BP control during the double-blind period: 33.6% vs. 23.4% at Week 2; 49.8% vs. 36.4% at Week 4, 58.0% vs. 37.0% at Week 8, 56.3% vs. 36.3% at Week 8 (LOCF) and 62.4% vs. 47.0% at Week 12. The confidence intervals either did not overlap [Weeks 4, 8, 8 (LOCF) and 12], or overlapped only slightly (Week 2).

Diastolic BP control was defined as MSDBP <90 mmHg. Compared to amlodipine, significantly greater numbers and proportions of patients receiving valsartan/amlodipine achieved diastolic BP control at each assessment during the double-blind period (54.9% vs. 44.2% at Week 2; 67.0% vs. 56.5% at Week 4; 70.0% vs. 57.4% at Week 8, 69.3% vs. 55.8% at Week 8 (LOCF) and 74.4% vs. 61.0% at Week 12.

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Patient Disposition:
Table 15 Number (%) of patients in analysis populations by treatment strategy

Population	Val/Aml n (%)	Amlodipine n (%)	Total n (%)
Screened			957
Randomized	322 (100.0)	324 (100.0)	646 (100.0)
Intent-to-treat	318 (98.8)	321 (99.1)	639 (98.9)
Safety	321 (99.7)	323 (99.7)	644 (99.7)
Per-protocol	272 (84.5)	275 (84.9)	547 (84.7)
ABPM	43 (13.4)	33 (10.2)	76 (11.8)

Demographic and Baseline Characteristics:

Table 16 Demographics by treatment strategy

Demographic Variable	Val/Aml 160/10mg N=322	Amlodipine 10mg N=324	Total N=646
Age (years)			
n	322	324	646
Mean (SD)	58.1 (10.24)	58.1 (10.44)	58.1 (10.33)
Range	32-84	28-89	28-89
Age Groups (years)			
<65	235 (73.0%)	234 (72.2%)	469 (72.6%)
≥ 65	87 (27.0%)	90 (27.8%)	177 (27.4%)
<70	274 (85.1%)	282 (87.0%)	556 (86.1%)
≥ 70	48 (14.9%)	42 (13.0%)	90 (13.9%)
<75	303 (94.1%)	303 (93.5%)	606 (93.8%)
≥ 75	19 (5.9%)	21 (6.5%)	40 (6.2%)
Gender			
Male	165 (51.2%)	159 (49.1%)	324 (50.2%)
Female	157 (48.8%)	165 (50.9%)	322 (49.8%)
Race			
Caucasian	261 (81.1%)	267 (82.4%)	528 (81.7%)
Other	23 (7.1%)	23 (7.1%)	46 (7.1%)
Asian	16 (5.0%)	21 (6.5%)	37 (5.7%)
Black	21 (6.5%)	12 (3.7%)	33 (5.1%)
Native American	1 (0.3%)	0 (0.0%)	1 (0.2%)
Pacific islander	0 (0.0%)	1 (0.3%)	1 (0.2%)
Ethnicity			
Other	206 (64.0%)	209 (64.5%)	415 (64.2%)
Hispanic/Latino	113 (35.1%)	111 (34.3%)	224 (34.7%)
Indian (Indian subcont.)	2 (0.6%)	3 (0.9%)	5 (0.8%)
Chinese	1 (0.3%)	0 (0.0%)	1 (0.2%)
Mixed ethnicity	0 (0.0%)	1 (0.3%)	1 (0.2%)
Height (cm)			
n	322	323	645
Mean (SD)	166.4 (10.41)	166.3 (9.67)	166.4 (10.04)
Range	142-196	140-198	140-198
Weight (kg)			
n	322	323	645
Mean (SD)	82.8 (17.50)	84.2 (19.41)	83.5 (18.48)
Range	50-146	40-191	40-191
BMI (kg/m2)			
n	322	323	645
Mean (SD)	29.8 (5.42)	30.3 (5.70)	30.1 (5.56)
Range	18-52	17-55	17-55

Table 17 Baseline disease characteristics by treatment strategy

Parameter	Val/Aml 160/10mg N=322	Amlodipine 10mg N=324	Total N=646
MSSBP (mmHg)			
n	322	324	646
Mean (SD)	170.2 (8.92)	170.9 (8.52)	170.5 (8.72)
Range	154-198	148-197	148-198
MSDBP (mmHg)			
n	322	324	646
Mean (SD)	95.6 (9.88)	94.7 (10.47)	95.2 (10.18)
Range	65-120	65-119	65-120
Sitting pulse (bpm)			
n	322	323	645
Mean (SD)	75.4 (12.16)	74.8 (12.03)	75.1 (12.08)
Range	46-130	43-110	43-130
Standing SBP (mmHg)			
n	313	320	633
Mean (SD)	166.8 (13.38)	166.2 (12.93)	166.5 (13.14)
Range	131-214	131-204	131-214
Standing DBP (mmHg)			
n	313	320	633
Mean (SD)	97.7 (11.46)	97.2 (11.23)	97.4 (11.34)
Range	63-132	57-124	57-132
Standing pulse(bpm)			
n	313	317	630
Mean (SD)	78.1 (12.65)	77.4 (12.36)	77.7 (12.50)
Range	48-132	46-124	46-132
Length of washout category (number of days)			
0 (naïve)	73 (22.7%)	57 (17.6%)	130 (20.1%)
3 (0-4 days)	161 (50.0%)	180 (55.6%)	341 (52.8%)
7 (≥ 5 days)	88 (27.3%)	87 (26.9%)	175 (27.1%)
Diabetes status			
No	287 (89.1%)	288 (88.9%)	575 (89.0%)
Yes	35 (10.9%)	36 (11.1%)	71 (11.0%)
ABPM participant			
No	271 (84.2%)	283 (87.3%)	554 (85.8%)
Yes	51 (15.8%)	41 (12.7%)	92 (14.2%)
Hypertension severity at baseline			
MSSBP < 180 mmHg	275 (85.4%)	268 (82.7%)	543 (84.1%)
MSSBP ≥ 180 mmHg	47 (14.6%)	56 (17.3%)	103 (15.9%)

Most patients had at least one past or continuing medical condition (74.2% for valsartan/amlodipine; 75.0% for amlodipine), which occurred at generally similar frequencies in both treatment strategies. The most frequently reported conditions (i.e., those reported for at least 15% of the patients in either treatment strategy) were metabolism and nutrition disorders (41.3% for valsartan/amlodipine; 42.6% for amlodipine), musculoskeletal and connective tissue disorders (28.6% for valsartan/amlodipine; 24.4% for amlodipine), surgical and medical procedures (21.4% for valsartan/amlodipine; 22.2% for amlodipine), gastrointestinal disorders (18.0% for valsartan/amlodipine; 17.9% for amlodipine), and nervous system disorders (16.5% for valsartan/amlodipine; 9.6% for amlodipine).

Primary efficacy results:
The primary efficacy variable was the change from baseline in MSSBP (mmHg) at Week 4. Patients who received valsartan/amlodipine exhibited significantly greater LSM reductions from baseline in MSSBP at Week 4 than did those who received amlodipine (30.1 mmHg and 23.5 mmHg, respectively). The difference in the reduction was statistically significant ($p < 0.0001$).

Table 18 Primary efficacy analysis: Change from baseline in MSSBP (mmHg) at Week 4 (LOCF) by treatment strategy (ITT population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=318)	318	170.2	-30.1 (0.79)	-6.6	(-8.59, -4.56)	<.0001*
Amlodipine (N=321)	321	170.8	-23.5 (0.81)			

N is the number of patients in the ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Table 19 Supportive primary efficacy analysis: Change from baseline in MSSBP (mmHg) at Week 4 (LOCF) by treatment strategy (Per-protocol population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=272)	272	170.3	-30.2 (0.84)	-6.3	(-8.38, -4.14)	<.0001*
Amlodipine (N=275)	275	170.7	-23.9 (0.85)			

N is the number of patients in per-protocol population; n is the number of per-protocol patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Secondary efficacy results:
Patients who received valsartan/amlodipine exhibited significantly greater LSM reductions from baseline in MSDBP at Week 4 (LOCF) than did those who received amlodipine (12.5 mmHg and 8.6 mmHg, respectively; p <0.0001).

Table 20 Change from baseline in MSDBP (mmHg) at Week 4 (LOCF) by treatment strategy (ITT population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=318)	318	95.7	-12.5 (0.44)	-3.9	(-5.05, -2.78)	<.0001*
Amlodipine (N=321)	321	94.7	-8.6 (0.45)			

N is the number of patients in ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is Val/Aml minus Amlodipine
ANCOVA model with treatment strategy, country and length of washout as factors and baseline MSDBP as covariate.
* p-value < 0.05

Additional analyses of MSSBP and MSDBP by week also showed significantly greater

reductions (p <0.0001) with valsartan/amlodipine than with amlodipine at each week of the double-blind period for both parameters. In both treatment strategies, the greatest reductions were achieved at Week 8.

Table 21 Change from baseline in MSDBP by week and treatment strategy (ITT population)

Timepoint	Treatment strategy	n	Baseline mean	LSM change (SEM)	Difference [1]	95% CI	p-value
Week 2	Val/Aml (N=318)	317	95.6	-9.0 (0.45)	-3.3	(-4.41, -2.12)	<.0001*
	Amlodipine (N=321)	320	94.6	-5.8 (0.46)			
Week 4	Val/Aml (N=318)	307	95.7	-12.9 (0.43)	-4.2	(-5.32, -3.10)	<.0001*
	Amlodipine (N=321)	307	94.9	-8.7 (0.45)			
Week 8	Val/Aml (N=318)	296	95.9	-13.9 (0.45)	-4.5	(-5.60, -3.32)	<.0001*
	Amlodipine (N=321)	299	94.8	-9.4 (0.45)			

N is the number of patients in the ITT population; n is the number of ITT patients with baseline and post-baseline non-missing values.
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is Val/Aml minus Amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSDBP as covariate.
* p-value < 0.05

Table 22 Change from baseline in MSSBP (mmHg) by week and treatment strategy (ITT population)

Timepoint	Treatment strategy	n	Baseline mean	LSM change (SEM)	Difference [1]	95% CI	p-value
Week 2	Val/Aml (N=318)	317	170.2	-23.3 (0.84)	-4.7	(-6.84, -2.57)	<.0001*
	Amlodipine (N=321)	320	170.8	-18.6 (0.86)			
Week 4	Val/Aml (N=318)	307	170.2	-30.7 (0.76)	-7.1	(-8.99, -5.13)	<.0001*
	Amlodipine (N=321)	307	170.8	-23.6 (0.78)			
Week 8	Val/Aml (N=318)	296	170.2	-32.0 (0.78)	-5.6	(-7.61, -3.63)	<.0001*
	Amlodipine (N=321)	299	170.7	-26.4 (0.79)			

N is the number of patients in ITT population; n is the number of ITT patients with baseline and post-baseline non-missing values.
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is Val/Aml minus Amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Sub-group analysis results:
As in the overall ITT population, subgroup analyses of the change from baseline in BP by severity of hypertension showed valsartan/amlodipine to be significantly more effective than amlodipine in reducing MSSBP and MSDBP at Week 4 of the double-blind period in patients with baseline MSSBP <180 mmHg. Similar results were shown in patients with baseline MSSBP ≥ 180 mmHg.

Table 23 Subgroup analysis: Change from baseline in MSSBP and MSDBP (mmHg) at Week 4 by treatment strategy and severity of hypertension at baseline (ITT population)

	MSSBP < 180 at baseline		MSSBP ≥ 180 at baseline	
	Val/Aml 160/10 mg	Amlodipine 10 mg	Val/Aml 160/10 mg	Amlodipine 10 mg
Statistic	N=272	N=266	N=46	N=55
MSSBP				
LSM change (SEM)	-28.7 (0.84)	-22.1 (0.87)	-40.1 (1.92)	-31.7 (1.94)
Difference [1]	-6.60		-8.42	
95% CI	(-8.71, -4.49)		(-13.62, -3.22)	
p-value	<.0001*		0.0018*	
MSDBP				
LSM change (SEM)	-12.4 (0.49)	-8.0 (0.51)	-14.6 (0.99)	-12.2 (1.01)
Difference [1]	-4.46		-2.47	
95% CI	(-5.70, -3.23)		(-5.11, 0.17)	
p-value	<.0001*		0.0667	

N is the number of patients in the ITT population.
LSM change = least squares mean change from baseline, SEM = standard error of the mean.
[1] Difference is Val/Aml 160/10 mg minus Amlodipine 10 mg.
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP or MSDBP as covariate.
* p-value < 0.05

Reviewer's comment:
The FDA statistical reviewer also conducted a sub-group analysis by region. The result showed patients who received valsartan/amlodipine exhibited greater reduction in change from baseline in MSSBP at week 4 than did those who received amlodipine in both U.S and non-US populations.

Sub-group Analysis by Region

Region	Treatment	N	Baseline Mean	LSM Change from Baseline	Difference	95% CI
US	Val/Aml	92	169.80	-32.16	-8.57	-12.35, -4.79
	Amlodipine	95	171.70	-23.59		
Non-Us	Val/Aml	226	170.33	-29.94	-5.99	-8.41, -3.56
	Amlodipine	226	170.45	-23.95		

Exploratory analysis results:
Overall blood pressure control was defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg. At Week 4 (LOCF), there were significantly greater proportions of patients who achieved overall blood pressure control in the valsartan/amlodipine group than in the amlodipine group (44.7% vs. 23.7%). This was also true at Weeks 2, 4 and 8.

Table 24 Proportion of unadjusted overall BP control by week and treatment strategy (ITT population)

Timepoint	Treatment	n	No. (%) of BP controlled [1]	95% CI*
Week 2	Val/Aml 160/10 mg (N=318)	317	91 (28.7)	(23.73, 33.69)
	Amlodipine 10 mg (N=321)	320	45 (14.1)	(10.25, 17.87)
Week 4	Val/Aml 160/10 mg (N=318)	307	139 (45.3)	(39.71, 50.85)
	Amlodipine 10 mg (N=321)	307	73 (23.8)	(19.02, 28.54)
Week 8	Val/Aml 160/10 mg (N=318)	296	157 (53.0)	(47.35, 58.73)
	Amlodipine 10 mg (N=321)	299	93 (31.1)	(25.86, 36.35)

N is the number of patients in ITT population; n is the number of ITT patients with a non-missing measurement at that timepoint.
[1] overall BP control defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg.
* The asymptotic confidence intervals are presented.

One hundred patients had been expected to undergo ABPM. Although 92 patients had ABPM at baseline, only 76 (43 in the valsartan/amlodipine group, and 33 in the amlodipine group) had both baseline and post-baseline assessments.

Results for the between-treatment analysis of mean ambulatory systolic and diastolic blood pressure showed that valsartan/amlodipine was significantly more effective than amlodipine at Week 4 for both parameters. This is consistent with the results observed for the change from baseline in MSSBP and MSDBP described above.

Table 25 Between treatment analysis results for change from baseline in mean ambulatory blood pressure at Week 4 by treatment strategy (ABPM population)

Variable	Treatment	Baseline mean	LSM change (SEM)	Difference [1]	95% CI	p-value
MASBP (mmHg)	Val/Aml 160/10 mg (N=43)	138.8	-15.68 (0.81)	-5.73	(-8.0,-3.5)	<.0001
	Amlodipine 10 mg (N=33)	137.5	-9.94 (0.86)			
MADBP (mmHg)	Val/Aml 160/10 mg (N=43)	82.0	-8.99 (0.51)	-4.10	(-5.5,-2.7)	<.0001
	Amlodipine 10 mg (N=33)	82.5	-4.89 (0.54)			

[1] Difference is val/aml 160/10 mg minus amlodipine 10 mg
Least square means and the associated standard errors, confidence intervals and p-values were from a repeated-measures analysis of covariance with treatment, country, length of washout, post dosing hour and treatment by post-dosing hour as fixed factors and baseline mean 24- hour ambulatory SBP as a covariate and autoregressive order 1 covariance structure (AR1).
*indicates statistical significance at 0.05 level.

Patients randomized in this study received either valsartan/amlodipine 160/5 mg or amlodipine 5 mg for two weeks, and then were force-titrated to receive an additional 5 mg of amlodipine at Week 4. They remained on this dose for the remaining 6 weeks of the 8-week double-blind period. Although both treatment strategies produced clinically meaningful reductions in blood pressure, valsartan/amlodipine combination therapy was reduced and controlled blood pressure at all efficacy measures and all timepoints.

6.1.5 Clinical Microbiology
NA

6.1.6 Efficacy Conclusions

Two studies (CVAA489A 2402 and CVAA489A2403) were submitted in this sNDA for efficacy in Stage II hypertension. Both studies showed valsartan/amlodipine improved efficacy over amlodipine alone. However, these studies are limited for several reasons which include the fact that Exforge is compared only to amlodipine, the primary endpoint is the reduction of the systolic blood pressure not the diastolic, and ultimately hydrochlorothiazide was added to patients who did not reach goal. Also, the placebo effect was not subtracted.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Valsartan has been marketed as monotherapy for hypertension since 1996 in doses up to 320 mg. Amlodipine is administered as monotherapy in doses up to 10 mg. Since approval as combination therapy in June 2007, there have been no new unexpected adverse reactions.

7.1.1 Deaths

There were no deaths in either study A2402 or A2403.

7.1.2 Other Serious Adverse Events

Table 26 Number (percent) of patients with most frequent AEs in Study A2402

Adverse events (Preferred terms)	Val/Aml N=286 n (%)	Amlodipine N=285 n (%)
Total no. (%) with AE(s)	127 (44.4)	129 (45.3)
Edema peripheral	36 (12.6)	27 (9.5)
Headache	12 (4.2)	15 (5.3)
Dizziness	7 (2.4)	7 (2.5)
Nausea	7 (2.4)	2 (0.7)
Edema	7 (2.4)	6 (2.1)
Nasopharyngitis	6 (2.1)	7 (2.5)
Bronchitis	4 (1.4)	0 (0.0)
Diarrhea	4 (1.4)	7 (2.5)
Fatigue	4 (1.4)	1 (0.4)
Gastritis	4 (1.4)	2 (0.7)
Influenza	4 (1.4)	1 (0.4)
Muscle spasms	4 (1.4)	6 (2.1)
Pain in extremity	4 (1.4)	5 (1.8)
Upper respiratory tract infection	4 (1.4)	6 (2.1)
Back pain	3 (1.0)	3 (1.1)
Erectile dysfunction	3 (1.0)	1 (0.4)
Pruritus	3 (1.0)	3 (1.1)
Rhinitis allergic	3 (1.0)	1 (0.4)
Sinus congestion	3 (1.0)	0 (0.0)
Arthralgia	2 (0.7)	5 (1.8)
Joint swelling	2 (0.7)	3 (1.1)
Neck pain	2 (0.7)	3 (1.1)
Pharyngolaryngeal pain	2 (0.7)	3 (1.1)
Pollakiuria	2 (0.7)	4 (1.4)
Sinusitis	2 (0.7)	3 (1.1)
Constipation	1 (0.3)	8 (2.8)
Dry mouth	1 (0.3)	3 (1.1)
Abdominal pain	0 (0.0)	3 (1.1)
Hypokalemia	0 (0.0)	9 (3.2)
Toothache	0 (0.0)	4 (1.4)

Table 27 Number (percent) of patients with most frequent AEs in Study A2403

Preferred term	Val/Aml N = 321 n (%)	Amlodipine N = 323 n (%)
Total no. (%) with an AE	113 (35.2)	120 (37.2)
Edema peripheral	41 (12.8)	57 (17.6)
Headache	12 (3.7)	10 (3.1)
Nasopharyngitis	9 (2.8)	6 (1.9)
Asthenia	5 (1.6)	1 (0.3)
Abdominal pain upper	4 (1.2)	1 (0.3)
Dizziness	4 (1.2)	1 (0.3)
Gastroenteritis	4 (1.2)	0 (0.0)
Joint swelling	4 (1.2)	3 (0.9)
Cough	3 (0.9)	5 (1.5)
Diarrhea	3 (0.9)	6 (1.9)
Urinary tract infection	2 (0.6)	4 (1.2)
Dyspepsia	1 (0.3)	4 (1.2)
Flushing	1 (0.3)	4 (1.2)
Hypokalemia	1 (0.3)	4 (1.2)

Reviewer's comment:
It is interesting to note in the above 2 tables in both studies it is apparent that there is a higher percent of patients with peripheral edam on the combination than with amlodipine alone.

7.1.3 Dropouts and Other Significant Adverse Events

Table 2 8 Number (percent) of patients who had SAEs in Study A2402

Total number of patients studied	Val/Aml N=286 n (%)	Amlodipine N=285 n (%)
Deaths	0 (0.0)	0 (0.0)
Patients with serious AEs:		
Non-fatal SAEs	3 (1.0)	3 (1.1)
Drug related SAEs	1 (0.3)	0 (0.0)
Patients with other significant AEs:		
AEs suspected to be study drug related	50 (17.5)	38 (13.3)
AEs leading to study drug dose adjustment/interruption	3 (1.0)	2 (0.7)
Discontinuations due to:		
Any AEs including SAEs	7 (2.4)	9 (3.2)
SAEs	1 (0.3)	0 (0.0)
AEs (non-serious)	6 (2.1)	9 (3.2)
AEs suspected to be study drug related	6 (2.1)	6 (2.1)

Table 29 Number (%) of patients who had SAEs and other significant AEs in Study A2403

Total number of patients studied	Val/Aml N=321 n(%)	Amlodipine N=323 n(%)
Deaths	0 (0.0)	0 (0.0)
SAEs	3 (0.9)	0 (0.0)
Discontinuations due to:		
Any AEs including SAEs	19 (5.9)	19 (5.9)
SAEs	3 (0.9)	0 (0.0)
AEs suspected to be study drug related	13 (4.0)	19 (5.9)
Patients with other significant AEs:		
AEs leading to study drug dose adjustment/interruption	6 (1.9)	4 (1.2)

The most frequently reported reasons for discontinuation were lost to follow-up, withdrawal of consent, AEs, and protocol deviations. Lost to follow-up occurred more often in the valsartan/amlodipine treatment strategy than in the amlodipine treatment strategy; other reasons for discontinuation occurred at similar frequencies in both treatment strategies.

7.1.3.3 Other significant adverse events

Table 30 Adverse events potentially related to low blood pressure Study A2402

	Val/Aml N=286	Amlodipine N=285
Dizziness	7 (2.4%)	7 (2.5%)
Orthostatic hypotension	1 (0.3%)	0 (0.0%)
Vertigo	1 (0.3%)	0 (0.0%)

Table 31 Adverse events potentially related to low blood pressure Study A2403

	Val/Aml N=321	Amlodipine N=323
Dizziness	4 (1.2%)	1 (03.%)
Syncope	3 (0.9%)	0 (0.0%)
Hypotension	1 (0.3%)	0 (0.0%)

7.1.7 Laboratory Findings

7.1.7.1 Study A2402:

In Study A2402 the mean and median changes from baseline at endpoint (Week 12) were clinically unremarkable in all treatment strategies for the hematology parameters. Also, in the biochemistry parameters both mean and median changes from baseline at Weeks 4, 8, 12 and endpoint were clinically the same in both groups. The biochemistry parameters with the largest proportions of patients with clinically notable abnormalities were BUN, calcium, glucose and potassium. Clinically notable decreases in calcium and increases in potassium were observed at similar frequencies in both treatment strategies. Clinically notable increases in BUN and calcium occurred more often in the valsartan/amlodipine treatment strategy than in the amlodipine treatment strategy. Clinically notable increases in glucose and bilirubin and decreases in potassium occurred more often in the amlodipine treatment strategy than in the valsartan/amlodipine treatment strategy.

7.1.7.2 Study A2403:

In Study A2403 mean and median changes from baseline at endpoint were clinically unremarkable in all treatment strategies for the hematology parameters. For the biochemistry parameters mean and median changes from baseline at endpoint were clinically unremarkable in both groups. The biochemistry parameters with the largest proportions of patients with clinically notable abnormalities were potassium and calcium. Clinically notable increases in calcium and potassium were observed at similar frequencies in both treatment strategies. Clinically notable decreases in potassium occurred more often in the amlodipine treatment strategy (9.8%) than in the valsartan/amlodipine treatment strategy (3.6%). Otherwise, the frequencies of patients exhibiting clinically notable changes from baseline were generally similar for both treatment strategies.

7.1.8 Vital Signs

7.1.8.1 Study A2402:

The incidence of patients with orthostatic blood pressures is summarized in the table below. A criteria of a decrease of at least 20 mmHg in systolic blood pressure or a decrease of at least 10 mmHg in diastolic blood pressure when a patient moves from a sitting position to a standing position was used to define orthostatic blood pressure changes. A total of 25 patients (8.7%) in the valsartan/amlodipine treatment strategy and 24 patients (8.4%) in the amlodipine treatment strategy met the criteria at any post-baseline visit. At the earliest evaluated timepoint of 2 weeks, the incidence rates were also comparable between groups.

Table 32 Frequency of orthostatic blood pressure changes in Study VAA2402

Timepoint	Val/Aml N=286 n (%)	Amlodipine N=285 n (%)
Any [1]	25 (8.7)	24 (8.4)
Week 2	8 (2.8)	10 (3.5)
Week 4	12 (4.2)	3 (1.1)
Week 8	6 (2.1)	9 (3.2)
Week 12	7 (2.4)	9 (3.2)
Endpoint [2]	10 (3.5)	10 (3.5)

Orthostatic blood pressure is defined as a reduction in MSSBP of at least 20 mmHg or a reduction in MSDBP of at least 10 mmHg immediately after standing (or 3 min after standing) compared to the measurements taken in sitting position.
[1] Orthostatic blood pressure at any post-baseline visit
[2] Endpoint is the value at Week 12 or LOCF value

7.1.8.2 Study A2403:

The incidence of orthostatic blood pressure changes was similar in both treatment strategies. Fourty-three patients (13.4%) in the valsartan/amlodipine treatment strategy and 47 patients (14.6%) in the amlodipine treatment strategy met the criteria at any post-baseline visit. Even at the early timepoints, the incidence rates were also comparable between groups as seen in the table below.

Table 33 Orthostatic blood pressure changes in StudyA2403

	Val/Aml (N=321)		Amlodipine (N=323)	
Timepoint	Base	Post	Base	Post
Baseline	44 (13.7)		30 (9.3)	
Any [1]	6 (1.9)	43 (13.4)	4 (1.2)	47 (14.6)
Week 2	4 (1.2)	18 (5.6)	1 (0.3)	18 (5.6)
Week 4	1 (0.3)	15 (4.7)	1 (0.3)	14 (4.3)
Week 8	2 (0.6)	16 (5.0)	3 (0.9)	19 (5.9)
Endpoint [2]	4 (1.2)	23 (7.2)	4 (1.2)	27 (8.4)

Orthostatic blood pressure is defined as a reduction in MSSBP of at least 20 mmHg or a reduction in MSDBP of at least 10 mmHg immediately after standing (or 3 min after standing) compared to the measurements taken in sitting position.
[1] Orthostatic blood pressure at any post-baseline visit
[2] Endpoint is the value at Week 8 or LOCF value

7.2 Safety Conclusion
The observed safety profile of initial therapy with valsartan/amlodipine is consistent with the known pharmacological response of an angiotensin receptor blocker (valsartan) and a calcium channel blocker (amlodipine). The overall incidence rates of AEs, SAEs and AEs leading to discontinuation were similar with valsartan/amlodipine administered as initial therapy compared to amlodipine monotherapy. The incidence of AEs potentially related to low blood pressure was low with combination therapy and comparable to amlodipine monotherapy.

9 OVERALL ASSESSMENT

9.1 Conclusions

This sNDA was first submitted as a change in the original label from treating patients for hypertension who did not reach control with either valsartan or amlodipine alone to treatment as initial therapy for hypertension. Two additional studies for Stage II hypertension were also submitted which are reviewed here. These studies are limited for several reasons which include the fact that Exforge is compared only to amlodipine, the primary endpoint is the reduction of the systolic blood pressure not the diastolic, and ultimately hydrochlorothiazide was added to patients who did not reach goal. Also, the placebo effect was not subtracted. Therefore, these reviewers believe that the label should include Exforge as initial treatment for hypertension but that these additional studies are only approvable.

9.2 Recommendation on Regulatory Action

Approvable

9.3 Recommendation on Postmarketing Actions

NA

9.4 Labeling Review

To be reviewed separately.

9.5 Comments to Applicant

NA

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/s/

Gail Moreschi
6/30/2008 01:33:00 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1

1. ORGANIZATION ONDQA		2. NDA NUMBER 21-990	
3. NAME AND ADDRESS OF APPLICANT (*City and State*) Novartis Pharmaceuticals Corporation One Health Plaza, East Hanover, NJ 07936-1080		4. AF NUMBER	
		5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG Exforge®	7. NONPROPRIETARY NAME Amlodipine besylate and Valsartan	SE1-003	09-24-2007
8. SUPPLEMENT PROVIDES FOR: The initial treatment of Hypertension.		9. AMENDMENTS DATES 01-29-2008	
10. PHARMACOLOGICAL CATEGORY Treatment of Hypertension	11. HOW DISPENSED RX ✓ OTC	12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Tablets	14. POTENCY 5/160, 10/160, 5/320 and 10/320 mg		

15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT

Amlodipine besylate:

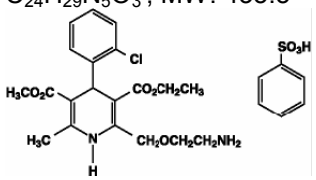
3-Ethyl-5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate

$C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ MW: 567.1

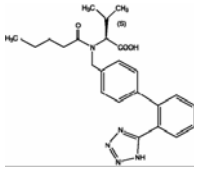
Valsartan:

N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine

$C_{24}H_{29}N_5O_3$, MW: 435.5



Amlodipine Besylate



Valsartan

16. RECORDS AND REPORTS

CURRENT YES__ NO
REVIEWED YES__ NO

17. COMMENTS

This drug is currently approved for the treatment of hypertension. The current application is to seek approval to use Exforge in the initial treatment of hypertension. No new CMC information was submitted in this application. There are no changes proposed to the "Description" and "How Supplied" sections of labeling.

The applicant submitted an environmental assessment document where the expected introduction concentration (EIC) for amlodipine and Valsartan are reported to be 0.25 ppb and 10.49 ppb respectively. Based on the above, a consult was sent to OPS to evaluate the EA document. Dr. Raanan Bloom is his review dated July 15th has determined no significant adverse environmental impacts are expected from the introduction of amlodipine and valsartan residues into the environment.

18. CONCLUSIONS AND RECOMMENDATIONS

Based on the above, this supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.

19. CHEMIST

NAME	SIGNATURE	DATE COMPLETED
Nallaperumal Chidambaram, Ph.D.		07-16-2008

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Chemist: N. Chidambaram Ph.D.	CSO: Q. nguyen HFD-110	Branch Chief: J. Vidra Ph.D.

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

/s/

Nallaperumal Chidambaram
7/17/2008 08:30:28 AM
CHEMIST

Jim Vidra
7/17/2008 11:10:42 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

EXFORGE® 5/160 , 10/160, 5/320 and 10/320 mg film-coated tablets

NDA 21-990

Food and Drug Administration
Center for Drug Evaluation and Research

July 14, 2008

FINDING OF NO SIGNIFICANT IMPACT

for

NDA 21-990

EXFORGE® 5/160 , 10/160, 5/320 and 10/320 mg film-coated tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and concluded that this action will not have a significant impact on the quality of the human environment. Therefore, an environmental impact statement will not be prepared.

In support of the new drug application, Norvartis Pharmaceutical Corporation prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 that evaluates the potential environmental impacts due to use and disposal of this product. The application requests the approval of an NDA supplement for fixed combinations of amlodipine and valsartan in EXFORGE® 5/160, 10/160, 5/320 and 10/320 mg film-coated tablets for the initial treatment of hypertension. Approval of the supplement is expected to benefit patients requiring more than one agent to control hypertension.

Results of the EA indicate no significant adverse environmental impacts are expected from the introduction of amlodipine and valsartan residues into the environment due to the use of EXFORGE® 5/160, 10/160, 5/320 and 10/320 mg film-coated tablets.

At U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital or clinic procedures. Empty or partially empty containers from home use will be disposed of through community solid waste management systems which typically include landfills, incineration, and recycling. Minimal quantities of unused drug are expected to be disposed of through sanitary sewer systems.

The Center for Drug Evaluation and Research has concluded that this product can be used and disposed of without any expected adverse environmental impacts. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY:

Raanan A. Bloom, Ph.D.
Senior Environmental Officer
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Jon Clark, M.S.
Associate Director for Policy
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

CONCURRED BY:

Moheb Nasr, Ph.D.
Director, Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment:

Environmental Assessment
Appended Electronic Signature Page

Global Pharma Environment

EXFORGE®
Valsartan / Amlodipine
(VAA489)

5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg film-coated tablets

EXFORGE_ABBR_EA_2

Environmental assessment

Authors: Hoeger Birgit

Date: 15-Jan-2008

Status: final

Number of pages: 14

1 Date

24-Jan-2008

EXFORGE sNDA submission 003, as supplement to NDA 21-990

Reference is made to Environmental Assessments submitted to related Exforge and Diovan NDAs:

Exforge Tablets, NDA 21-990

Original NDA submission:	Document dated 22-Feb-2006

Diovan Capsules, NDA 20-665

Original NDA submission:	Document dated 20-Nov-1995
Amendment original NDA:	Submitted 30-May-1996
Amendment original NDA:	Submitted 22-Oct-1996

Diovan HCT Tablets, NDA 20-818

Original NDA approval :	06-Mar-1998
Supplement (S-012):	Document dated 14-Sep-2001

Diovan Tablets, NDA 21-283

Original NDA submission:	Document dated 03-Aug-2000
Supplement (S-001):	Document dated 05-Jul-2001
Supplement (S-011)	Document dated 31-Oct-2003

All environmental fate and effects study reports for valsartan drug substance previously submitted to the Diovan Capsule NDA 20-665 and reviewed by the Agency have not been included in this Assessment.

2 Name of applicant/petitioner

Novartis Pharmaceuticals Corporation

3 Address

One Health Plaza
East Hanover, NJ 07936-1080

4 Description of proposed action

4.1 Requested approval

Novartis has filed an supplemental NDA pursuant to section 505b of the FD&C Act for EXFORGE (amlodipine and valsartan) 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg film-coated tablets. An Environmental Assessment (EA) is submitted pursuant to 21 CFR part 25.

4.2 Need for action

Amlodipine and valsartan are currently approved separately, as well as in combination in various dosage forms and strengths for the treatment of hypertension. This supplement provides for fixed combinations of amlodipine and valsartan in the form of 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg film-coated tablets, for the initial treatment of hypertension. Approval of this submission is expected to benefit patients unlikely to achieve control of blood pressure with a single agent.

4.3 Locations of use

Patients with hypertension will use EXFORGE film-coated tablets in their homes, in clinics and in hospitals.

4.4 Disposal sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages of drug product according to their internal established procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

5 Identification of substances that are the subject of the proposed action

a) Amlodipine besylate

5.1 Nomenclature

5.1.1 Established name (U.S. Adopted Name – USAN)

Amlodipine besylate

5.1.2 Chemical name

5.1.2.1 Chemical Abstracts Index name

5.1.2.2 3-Ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate

5.1.2.3 Systemic chemical name (IUPAC)

Benzenesulfonate2-[4-(2-chloro-phenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydro-pyridin-2-ylmethoxy]-ethyl-ammonium

5.1.3 Other names

UK 48340-26

5.2 Chemical Abstract Service (CAS) registration number

111470-99-6

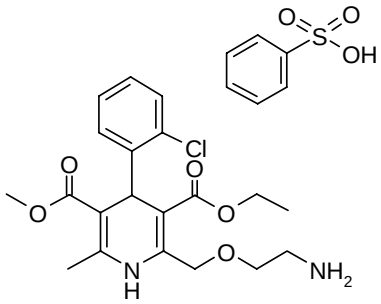
5.3 Molecular formula

C_{20} H_{25} Cl N_2 O_5 . C_6 H_6 O_3 S

5.4 Molecular weight

567.06

5.5 Structural formula



b) Valsartan

5.6 Nomenclature

5.6.1 Established name (U.S. Adopted Name – USAN)

Valsartan

5.6.2 Trade name

Diovan®

5.6.3 Chemical names

5.6.3.1 Chemical Abstracts Index name

L-Valine, *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-

5.6.3.2 Systematic chemical name (IUPAC)

(S)-2-{*N*-(1-oxopentyl)-*N*-[[2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl]methyl]-amino}-3-methyl-butyric acid

5.6.4 Other names

CGP 48933 (research code)

5.7 Chemical Abstracts Service (CAS) registration number

137862-53-4

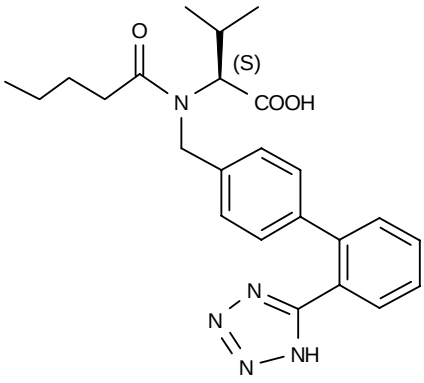
5.8 Molecular formula

$C_{24}H_{29}N_5O_3$

5.9 Molecular weight

435.5

5.10 Structural formula



6 Environmental issues

6.1 Physical and chemical characterization

Valsartan

All environmental fate and effects study reports for valsartan drug substance have been previously submitted to and reviewed by the Agency and have not been included in this Assessment: NDA 20-665 (submitted 28-Dec-1995; approved by FDA on 23-Dec-1996), NDA 20-818 (submitted 18-Mar-1997, approved 6-Mar-98) and NDA 21-283 (submitted 03-Aug-2000, approved 14-Aug-2002). The Data is summarized in a Summary Table (Table 1) located at the end of this report.

Based on its low log P [log K_{ow}] value, valsartan is not expected to significantly bioconcentrate in living organisms or to sorb to organic particles. Since the log K_{ow} was less than 3 at all pH levels tested, no further sorption/desorption properties (log K_{oc}) were considered. Based upon the Henry's Law Constant, valsartan would not be expected to be released into the air or have a significant vapor pressure. The valsartan information is summarized in a Data Summary Table (Table 1) located at the end of this report.

Amlodipine besylate

Environmental fate and effects study reports for amlodipine drug substance have been initially reported to the agency in Pfizer's Norvasc (amlodipine besylate) Tablets Original NDA 19-787 (approved 5-12-1995) and numerous submitted and approved supplement NDAs (not listed individually). This information has been previously submitted to and reviewed by the Agency, and is not included in the present assessment. The information is summarized in Data Summary Table (Table 2) located at the end of this report.

6.2 Environmental depletion mechanisms

Valsartan

Valsartan is hydrolytically stable at pH 5, 7 and 9 and was found not to be biodegradable aerobically or anaerobically to any significant extent. Since the molecule does not absorb light above 290 nm, photoinstability is not regarded a relevant environmental depletion mechanism. Results are reported in the Data Summary Table (Table 1).

Amlodipine besylate

Amlodipine shows some acute aquatic toxicity, and also has some potential to inhibit the microbial activity of activated sludge at high concentrations [Kumar et al. 2003]. It is not

readily biodegradable. Amlodipine is not expected to bioaccumulate, based on its physico-chemical properties and its high susceptibility to oxidative metabolism in higher organisms [CTD 2.5 Clinical Overview]. According to the original manufacturer, it has a tendency to sorb to sludge and sediments [Pfizer MSDS 2003].

Based on the UV/VIS absorption spectra [Drug substance elucidation of structure and other characteristics, Module 3], significant absorption is seen above 290 nm for amlodipine and photolability has actually been found for this compound. Hydrolytically, amlodipine has been found to be stable at environmental pH [Abdoh et al. 2004].

6.3 Environmental concentration

6.3.1 Expected Introduction Concentration (EIC)

As described in the July 1998 Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications[3], the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment may be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D

where:

A = kg / yr produced for direct use (as active moiety)

B = 1 / 1.214 x 10^{11} liters per day entering POTWs [1996 Needs Survey, Report to Congress]

C = 1 year / 365 days per year

D = 10^{9} µg/kg (conversion factor)

The EIC of amlodipine and valsartan has been calculated for the peak production year estimates of the drug substance requirements for all Novartis products containing amlodipine and valsartan, including the new EXFORGE formulations, and for all approved indications. An estimate of drug substance production requirements for the peak years (2010/2011) is presented in [Confidential Appendix 11.2.1]. The calculated EICs for amlodipine and valsartan are provided in [Confidential Appendix 11.2.2].

Novartis is confident that the actual EIC will not exceed these estimates by an order of magnitude.

As set forth in 21 CFR Part 25.31(b), action on an New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). “Increased use”, as defined in 21 CFR Part 25.5(a), will occur if the drug is “administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity.”

Novartis certifies that this submission for EXFORGE film-coated tablets, for the treatment of hypertension qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the concentration of the active moiety amlodipine will be significantly less than 1 ppb.

Further, Novartis states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment for amlodipine.

6.4 Summary

6.4.1 Valsartan - aquatic environment

Valsartan is pharmacologically active and is rapidly absorbed following oral administration. Since valsartan exists as a di-anion with a double negative charge at physiological pH, the compound is very hydrophilic, and may therefore be a poor substrate for metabolizing enzymes.

A study using radiolabeled valsartan solution showed that valsartan is metabolized to a small extent only. The only notable metabolite detectable in the plasma is the valeryl-4-hydroxy valsartan (M1), an oxidized form of valsartan. Since this metabolite has not demonstrated any pharmacological activity *in vitro*, the biotransformation of valsartan to M1 can be described as an additional minor elimination process.

Valsartan is predominantly excreted as unchanged drug through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified compounds in the feces and urine.

Studies were conducted to determine the water solubility and partition coefficient of valsartan at pH 5.0, 7.0 and 9.0 at 25 $\pm$ 2 °C (Data Summary Table 1). The results of the water solubility study indicate that valsartan would be relatively soluble in water over the environmental pH range. The n-octanol/water partition coefficient, which indicates the tendency of a non-ionized organic chemical to accumulate in fatty tissue and to sorb onto soil particles or other organic matter, suggests that valsartan would not be expected to sorb significantly to the organic material in soil or sediment, and would not be expected to bioconcentrate substantially in aquatic organisms. (Chemicals with a log P less than 1 are not expected to significantly bioconcentrate or sorb, whereas chemicals with a log P greater than or equal to 4 may be expected to bioconcentrate or sorb significantly.) The calculated results presented in Table 3 for the bioconcentration factor (BCF) and in Table 4 for the soil adsorption coefficient (K_{oc}) further support the conclusion that valsartan would be expected to remain mobile in the aquatic compartment, and would not be expected to bioconcentrate or bioaccumulate.

Results of the ultraviolet/visible spectra scan indicated absorbance below 290 nm in aqueous buffer solutions over the environmental pH range. Direct photodegradation would not be considered a potential mechanism of depletion.

Investigations of environmental depletion mechanisms demonstrated that valsartan would be hydrolytically stable over the environmental pH range at 50°C, and would not be expected to biodegrade under either aerobic or anaerobic conditions during waste water treatment.

Five-year production estimates for Diovan drug products indicate that during the peak year, the EIC of valsartan at the point of entry into the aquatic environment will be significantly greater than 1 ppb.

Based upon these factors, the evaluation of the environmental effects of the pharmacologically active parent compound, valsartan, was limited to the aquatic environment.

6.5 Valsartan - environmental effects of released substances

The environmental effects of valsartan were evaluated in the aquatic environment following the "Tiered Approach to Fate and Effects Testing" (Figure 1, July 1998 EA Guidance for Industry[3]). With no rapid, complete environmental depletion mechanism identified, microbial inhibition was evaluated in accordance with Technical Assistance Document (TAD), Section 4.02[4]. Additionally, acute toxicity testing was conducted in algae, daphnia and fish, utilizing standard methods according to either TAD 4.08[4], EU standard methodology[5] or OECD guidelines respectively. All studies were conducted under FDA Good Laboratory Practices (GLPs). Results indicate valsartan is non-inhibitory to microorganisms, which may be found in activated sludge and does not show deleterious effects on algae, daphnia and fish up to high concentrations. Algae proved to be the most sensitive species, with an EC_{50} of 90 mg/L. Results are reported in the Data Summary Table (Table 1).

6.5.1 Valsartan - assessment factor

As described in the July 1998 Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications[3], an Assessment Factor is a toxicity ratio which provides a consistent regulatory basis for determining if and when additional ecotoxicity testing should be performed, using a tiered approach. The Assessment Factor may be calculated by dividing an appropriate acute toxicity test endpoint by the MEEC (Maximum Expected Environmental Concentration). An Assessment Factor greater than 1000 would not require additional ecotoxicity testing.

In the case of valsartan, by applying the 72-hour EC_{50} from the green algae study and the EIC from [Confidential Appendix 11.2.2], an Assessment Factor of 8,571 is obtained. (Calculation of the Assessment Factor is provided in [Confidential Appendix 11.2.3]). Thus, no additional ecotoxicity testing would be required for valsartan. Since the Assessment Factor calculated for valsartan is 8 times greater than that reported in the Guidance Document, the results suggest valsartan is unlikely to be toxic in the aquatic environment.

7 Mitigation measures

Based upon the information and data presented in this environmental assessment, Novartis has concluded that no potential adverse environmental impacts are foreseen with the packaging, distribution, use or disposal of EXFORGE film-coated tablets within the United States. No mitigation measures are considered necessary.

8 Alternatives to the proposed action

No alternatives to the proposed action are suggested, as no potential adverse environmental impacts have been identified for the packaging, distribution, use or disposal of EXFORGE film-coated tablets. The use of EXFORGE film-coated tablets will directly benefit patients with hypertension.

It is our conclusion that approval of this application is therefore preferable to non-approval.

9 List of preparers

Curriculum vitae, documenting the qualifications and credentials of the contributors to this environmental assessment, are provided in [Non-confidential Appendix 11.1.1].

10 References

1. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, TAD Sections 3.01, 3.02, 3.03, 3.04, and 3.05.
2. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 3.09 and 3.11 (modified).
3. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), July 1998. Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications. CMC 6, Revision 1.
4. US FDA, March 1987. Environmental Assessment Technical Assistance Handbook, Sections 4.02 and 4.08.
5. Annex V to EU Directive 67/548/EEC, Part C. Available online at: http://ecb.jrc.it/testing-methods/ (accessed January 2006).
6. Abdoh, A., Al-Omari, M.M., Badwan, A.A., Jaber, A.M.Y. 2004. Amlodipine Besylate–Excipients Interaction in Solid Dosage Form. Pharmacol Dev Technol 9 :15-24 (2004)
7. Kumar, K.A., Ganguly, K., Mazumdar, K., Dutta, N.K., Dastidar, S.G., Chakrabarty, A.N. 2003. Amlodipine: a cardiovascular drug with powerful antimicriobial property. Acta Microbiol Pol 52:285-92 (2003).
8. Pfizer MSDS 2003. Official Material Safety Data Sheet for Amlodipine besylate. Last Revision Date: Jan 31 2003.

9. Kenaga, E.E., Goring, C.A.I., 1980. Relationship between water solubility, soil sorption, octanol-water partitioning, and concentration of chemicals in biota. American Society for Testing and Materials Spec. Tech. Publ. 707, Aquat. Toxicol., pp. 78-115.

11 Appendices

11.1 Non-confidential appendices

[11.1.1] Curriculum vitae of contributor

11.2 Confidential appendices

[11.2.1] Production estimates of amlodipine and valsartan drug substance requirements

[11.2.2] Expected Introduction Concentration (EIC) of amlodipine and valsartan based upon production estimates

[11.2.3] Calculation of assessment factor for valsartan

Table 1 Data summary table – valsartan

DATA SUMMARY TABLE		
ENDPOINT	RESULTS	METHODOLOGY
Water solubility – mean (mg/L)	2990 @ pH 5 8210 @ pH 7 1470 @ pH 9	TAD Section 3.01
Dissociation constants (mean pKa's)	3.76 (carboxylic group) and 5.60 (tetrazole group)	TAD Section 3.04
Log n-octanol/water partition coefficient (Log K_{ow})	1.51 @ pH 5 in 9.85 x 10^{-4} moles/L buffer 1.50 @ pH 5 in 1.07 x 10^{-4} moles/L buffer -1.17 @ pH 7 in 1.04 x 10^{-3} moles/L buffer -1.01 @ pH 7 in 1.09 x 10^{-4} moles/L buffer -1.84 @ pH 9 in 1.04 x 10^{-3} moles/L buffer -1.74 @ pH 9 in 1.10 x 10^{-4} moles/L buffer	TAD Section 3.02
Henry's Law Constant (H)	< 1.30 x 10^{-8}	TAD Section 3.03
Ultraviolet-visible absorption spectrum	No absorption peaks @ pH 5. One main peak at 209 nm @ pH 7. One main peak at 207 nm @ pH 9.	TAD Section 3.05
DEPLETION MECHANISMS		
Hydrolysis	t ½ $\geq$ 1 year at 25 °C	TAD Section 3.09
Aerobic biodegradation	0.02 % ^{14}C evolved over 28-day aerobic study	TAD Section 3.11, modified
Metabolism	Valsartan is predominantly excreted unchanged through feces, most likely via biliary elimination. Excretion is 99% complete within 7 days. Renal excretion, which accounts for 5 to 13% of the oral dose, is essentially complete within 48 hours. The bulk of the dose (83%) is excreted with the feces within 4 days. About 81% of the dose is excreted as unchanged valsartan, 9% as the valeryl-4-hydroxy metabolite (M1) and about 6% as other unidentified	Clinical studies

	compounds in the feces and urine.	
ENVIRONMENTAL EFFECTS		
Microbial inhibition	**Species** **MIC (mg/L)** *Aspergillus niger* > 1000 *Trichoderma viride* > 1000 *Clostridium perfringens* > 1000 *Bacillus subtilis* 1000 *Nostoc* sp. 200	TAD section 4.02
Algae toxicity (green algae)	EC_{50} (72h) = 90 mg/L NOEC = 58 mg/L	EU standard method 92/69/EC (L383) C.3 * Algal inhibition test.
Acute toxicity in *Daphnia magna*	EC_{50} (48h) = 580 mg/L NOEC = 280 mg/L	TAD 4.08
Acute toxicity in *Salmo gairdneri* (= *Oncorhynchus mykiss*, rainbow trout)	LC_{50} (96h) >100 mg/L NOEC = 100 mg/L	OECD 203, Fish, acute toxicity test (1992)

Table 2 Data summary table - amlodipine

DATA SUMMARY TABLE		
ENDPOINT	RESULTS	METHODOLOGY
Water solubility – mean (mg/L)	Slightly soluble (0.2%, w/v, 24°C)	source: Pfizer
Dissociation constants (mean pKa's)	8.6 (primary amine)	source: Pfizer
Log n-octanol/water partition coefficient (Log K_{ow})	2.759 (at 20° C, pH 7)	source: Pfizer
Henry's Law Constant (H)	Negligible vapour pressure (MP = 199.4°C)	source: Pfizer
Ultraviolet-visible absorption spectrum	Maxima at 240nm, 360 nm	source: Pfizer
DEPLETION MECHANISMS		
Hydrolysis	<10% (8d, RT, pH 7, 0.2M phosphate buffer)	Abdoh et al., Pharmacol Dev Technol 9 :15-24 (2004)
Aerobic biodegradation	Not readily biodegradable	source: Pfizer
Metabolism	Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites	Clinical studies

	excreted in the urine.	
ENVIRONMENTAL EFFECTS		
Microbial inhibition	**Species** **MIC (mg/L)** *E. coli* 10mg/l *Pseudomonas putida* 10mg/l *Bacillus spp*. 10 mg/l	Agar plate dilution method. Kumar et al., Acta Microbiol Pol 52:285-92 (2003)
Algae toxicity (green algae)	EC_{50} (72h) = 5.6 mg/L	NPDES, Source: Pfizer
Acute toxicity in *Daphnia magna*	EC_{50} (48h) = 9.9 mg/L	TAD 4.08 / OECD, Source: Pfizer
Acute toxicity in *Pimephales promelas* (fathead minnow)	LC_{50} (48h) 2.7 mg/L	NPDES, Source: Pfizer

12 Calculated environmental fate results for valsartan

Table 3 Calculated results for bioconcentration factor (BCF) and soil absorption coefficient (K_{oc}) for valsartan based upon experimentally determined water solubility

	pH 5	pH 7	pH 9
Water solubility (mg/L)	2990	8210	1470
BCF [a]	6.77	3.83	10.12
K_{oc} [b]	53.5	30.7	79.1

[a] Log (BCF) = 2.791 – 0.564 Log (S), where S = water solubility in mg/L.

[b] Log (K_{oc}) = 3.64 – 0.55 Log (S), where S = water solubility in mg/L.

Table 4 Calculated results for bioconcentration factor (BCF) and soil adsorption coefficient (K_{oc}) for valsartan based upon experimentally determined partition coefficient (log K_{ow})

	Range	
	Low	**High**
BCF [a]	0.014	6.21
K_{oc} [b]	2.38	158

The lowest (-1.84) and highest (1.51) log K_{ow} values were used to calculate the BCF and K_{oc}.

[a] Log (BCF) = (0.79 x log K_{ow}) – 0.40 (Kenaga and Goring, 1980)

[b] Log (K_{oc}) = (0.544 x log K_{ow}) + 1.377 (Kenaga and Goring, 1980)

Birgit Hoeger, Ph.D.

Global Pharma Environment

Relevant Professional Experience

2006 - Environmental Risk Assessment Officer at Novartis Pharma AG.

2005-2006 Contractual Agent at the European Commission - Joint Research Centre, Ispra, Italy, European Centre for the Validation of Alternative Methods (ECVAM), Task Officer for Environmental Toxicology.

2004-2005 Postdoctoral student, Environmental Toxicology, University of Konstanz (Prof. Dr. D.R. Dietrich). Toxicological investigations on bioconcentration of human pharmaceuticals and their effects on the immune system in brown trout (*Salmo trutta f. fario*).

Education

2004 Ph.D. Biology (Environmental Toxicology) at the University of Konstanz, Germany (Prof. Dr. D.R. Dietrich). Effects of sewage treatment plant effluent on the immune system of rainbow trout (*Oncorhynchus mykiss*).

2000 Diplom in Biology, University of Konstanz, Germany.

Publications

> 6 peer reviewed publications
Co-author of several project reports and a book chapter on effects of pollution of the aquatic environment on the immuno-competence of fishes.

Professional Memberships

SETAC (Society of Environmental Toxicology and Chemistry (2006 -)
Reach Implementation Project 3.3-2, Endpoint Working Group 10 (Aquatic Bioaccumulation and Avian Toxicity) (2006 - 2007)

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/s/

Jon E. Clark
7/16/2008 09:41:43 AM

Moheb Nasr
7/18/2008 08:16:26 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: July 14, 2008

From: Raanan A. Bloom, Ph.D.
OPS/IO/PARS

To: Swati Patwardhan
OPS/ONDQA

Through: Jon Clark, M.S.
OPS/IO/PARS

Subject: **NDA 21-990**; EXFORGE® (amlodipine, valsartan) 5/160, 10/160, 5/320 and 10/320 mg film-coated tablets

Novartis Pharmaceutical Corporation
One Health Plaza
East Hanover, NJ

Background

Novartis Pharmaceutical Corporation is requesting approval of an NDA supplement for fixed combinations of amlodipine and valsartan in EXFORGE® 5/160, 10/160, 5/320 and 10/320 mg film-coated tablets for the initial treatment of hypertension. Approval of the supplement is expected to benefit patients requiring more than one agent to control hypertension. An Environmental Assessment (EA) has been submitted pursuant to 21 CFR part 25.

Discussion

The EA requests a categorical exclusion under 21CFR25.31(b) for amlodipine. Based on the provided information the EIC of amlodipine is 0.25 ppb. Additional data are not required for amlodipine and an exclusion is applicable. Accordingly, the EA assesses the environmental impact of valsartan. The EIC of valsartan for all supplements under this NDA is calculated to be 10.49 ppb.

The original NDA for EXFORGE Tablets was submitted on Feb. 22, 2006. The 12/08/06 CMC review indicated that the submitted EA was adequate and concluded that no environmental impacts are expected due to approval of the NDA. The EIC for valsartan as

presented in the original NDA EA was 8.5 ppb. Comparison to the most sensitive species (algae toxicity; EC_{50}= 90 mg/L) gave an assessment factor of 10,000. With the addition of the present supplement the assessment factor is calculated as 8,571. According to CDER EA guidelines additional toxicity studies are not required for an assessment factor greater than 1000. The conclusions of the original NDA CMC EA review remain valid.

In addition, valsartan EAs and environmental fate and effects studies for valsartan were previously submitted under NDA 20-665 (Diovan Capsules). Additional EAs were submitted and accepted under NDA 20-818 (Diovan HCT Tablets) and NDA 21-283 (Diovan Tablets).

Comments and Conclusions

Based on an evaluation of the information provided in this EA and previous EAs and in FDA guidance, and on the scientific validity of the "no effects" conclusions of the EA, no significant adverse environmental impacts are expected from the introduction of amlodipine and valsartan residues into the environment due to the use of EXFORGE® 5/160, 10/160, 5/320 and 10/320 mg film-coated tablets.

A Finding of No Significant Impact (FONSI) is recommended. The FONSI is applicable to the combination product.

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/s/

Raanan Bloom
7/15/2008 12:31:49 PM
ENV ASSESSMENT

Jon E. Clark
7/16/2008 09:41:23 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

STATISTICAL REVIEW(S)

CLINICAL and STATISTICAL REVIEW

Application Type	NDA 21-990
Submission Number	S-003
Submission Code	
Letter Date	September 24, 2007
Stamp Date	
PDUFA Goal Date	July 24, 2008
Reviewers Names	Gail Moreschi, MD, MPH Ququan Liu, MD, MS
Review Completion Date	June 30, 2008
Established Name	amlodipine besylate & valsartan
Trade Name	Exforge
Therapeutic Class	Dihydropyridine CCB/ARB
Applicant	Novartis
Priority Designation	S
Formulation	Combination tablets
Dosing Regimen	Once daily
Indication	Hypertension
Intended Population	Adults

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1 EXECUTIVE SUMMARY

This sNDA was first submitted as a change in the original label from treating patients for hypertension who did not reach control with either valsartan or amlodipine alone to treatment as initial therapy for hypertension. Two additional studies for Stage II hypertension were also submitted which are reviewed here. These studies are limited for several reasons which include the fact that Exforge is compared only to amlodipine, the primary endpoint is the reduction of the systolic blood pressure not the diastolic, and ultimately hydrochlorothiazide was added to patients who did not reach goal. Also, the placebo effect was not subtracted. Therefore, these reviewers believe that the label should include Exforge as initial treatment for hypertension but that these additional studies are only approvable.

1.1 Recommendation on Regulatory Action

Approvable

1.2 Recommendation on Postmarketing Actions

NA

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This sNDA is primarily label change seeking initial treatment for hypertension. The Sponsor has also submitted two studies from the ongoing development program.

1.3.2 Efficacy

The two studies reviewed here were in patients with Stage II hypertension, not severe hypertension. The systolic blood pressure was the primary index followed. In some patients HCTZ was added in order to control the blood pressure.

1.3.3 Safety

In this submission there are no new safety findings. However, it is interesting that peripheral edema occurred more often with valsartan/amlodipine combination than with amlodipine alone.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Valsartan has been marketed as monotherapy for hypertension since 1996 in doses up to 320 mg. Amlodipine is administered as monotherapy in doses up to 10 mg. Since approval as combination therapy in June 2007, there have been no new unexpected adverse reactions.

2.2 Currently Available Treatment for Indication

Avalide (irbsarten/HCTZ; NDA 20-758/S-037) has been approved as initial therapy for hypertension.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Please refer to original NDA 21-990

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The Sponsor submitted the updated label and two additional studies from their ongoing developmental program.

4.2 Table of Clinical Studies

Ref.	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
report: Doc. **listings:** Doc.	**protocol:** VAA489A2402 **invest.:** Flack J **countries:** Columbia, Ecuador, South Africa, US **start:** 8 June 2006 **end:** 16 Apr 2007 **publ.:** None	**design, goal & population:** A 12-week DB, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered val/aml combination based therapy versus aml monotherapy in Black patients with stage II hypertension. Patients whose BP is not at target (≥130 mmHg MSSBP) after 8 weeks of DB treatment can have HCTZ added. **evaluations:** Primary: Change from baseline in MSSBP. Secondary: Change from baseline in MSDBP, BP control rate (MSSBP < 140 mmHg and MSDBP < 90 mmHg). Safety: AEs/SAEs, PE, vital signs, lab values, urinalysis, ECG, pregnancy test	**total:** 572 randomized, 497 complete, 75 discontinued **age:** ≥ 18; mean age = 53.2 yrs (228 male, 344 female) **groups:** 2 (patients are to be randomized in equal numbers)	**form:** capsule + tablet **route:** p.o. **regimen:** o.d. **duration:** 1-3 to 7 day screening/ washout 12 week DB treatment **doses:** Val/Aml 160/5 mg (2 wks) then force titration to 160/10 mg (2 wks) then optional titration to 320/10 mg (4 wks) then optional addition of HCTZ 12.5 mg (4 wks). Aml 5 mg (2 wks) then force titration to Aml 10 mg (2 wks) then optional sham titration to Aml 10 mg (4 wks) then optional addition of HCTZ 12.5 mg (4 wks)	**status:** Completed **report:** Published **general results:** The Valsartan/Amlodipine combination treatment regimen produced a statistically significantly greater reduction in MSSBP from baseline compared to Amlodipine monotherapy at Week 8 (33.3 mmHg for Valsartan/Amlodipine; 26.6 mmHg for Amlodipine (p<0.05).

Ref.	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status Type of Report General Results
report: Doc. **listings:** Doc.	**protocol:** VAA489A2403 **invest.:** Destro M **countries:** Belgium, Denmark, Italy, Mexico, Poland, Spain, US **start:** 9 Jun 2006 **end:** 10 Apr 2007 **publ.:** None	**design, goal & population:** An 8 - week DB, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered val/aml combination based therapy versus aml monotherapy in patients with stage II hypertension. Patients whose BP is not at target (≥130 mmHg) after 4 weeks of DB treatment can have HCTZ added. **evaluations:** Primary: Change from baseline in MSSBP. Secondary: Change from baseline in MSDBP, BP control rates. ABPM Substudy. Safety: AEs/SAEs, PE, vital signs, lab values, urinalysis, ECG, pregnancy test	**total:** 646 randomized, 577 complete, 69 discontinued (528 w, 33b, 37 a, 48 o) **age:** ≥ 18; mean age = 58.1 yrs; (324 male, 322 female) **groups:** 2 (patients are to be randomized in equal numbers)	**form:** capsule + tablet **route:** p.o. **regimen:** o.d. **duration:** 1-3 to 7 day screening/ washout 8 week DB treatment **doses:** Val/Aml 160/5 mg (2 wks) then force titration to 160/10 mg (2 wks) then optional addition of HCTZ 12.5 mg (4 wks). Aml 5 mg (2 wks) then force titration to Aml 10 mg (2 wks) then optional addition of HCTZ 12.5 mg (4 wks).	**status:** Completed **report:** Published **general results:** Patients who received Valsartan/Amlodipine exhibited a significantly greater LSM reduction from baseline in MSSBP at Week 4 (LOCF) than did those who received Amlodipine (30.1 mmHg and 23.5 mmHg, respectively; p<0.05).

4.3 Review Strategy

This was a joint review shared between the statistical and medical reviewers.

4.4 Data Quality and Integrity

A DSI inspection was not warranted.

4.5 Compliance with Good Clinical Practices

The studies were performed in accordance with standard operating procedures of the Sponsor. They were designed to ensure adherence to GCP and to ensure the protection of the patients.

4.6 Financial Disclosures

There were no unusual finical disclosures determined.

5 CLINICAL PHARMACOLOGY

Please refer to original NDA 21-990

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Two studies (CVAA489A 2402 and CVAA489A 2403) were submitted with an updated label seeking initial treatment for hypertension. These studies will be presented separately as the populations studied were different.

6.1.1 Methods

Both Studies A2402 and A2403 were double-blind, randomized, multicenter, parallel group studies evaluating the safety and efficacy of orally administered valsartan/amlodipine combination based therapy versus amlodipine in patients with Stage II hypertension. Study A2402 was completed in Black patients.

6.1.2 General Discussion of Endpoints

The endpoint was that the combination of valsartan/amlodipine produces a superior reduction in the mean sitting systolic blood pressure (MSSBP) from baseline compared to amlodipine.

6.1.3 Study Design

6.1.3.1. Study CVAA489A 2402

Title: A 12-week double-blind, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered valsartan/amlodipine combination based therapy versus amlodipine monotherapy in Black patients with stage II hypertension

Study dates: June 8, 2006 to April 16, 2007

Phase IIIb

Study Centers: A total of 74 centers in 4 countries enrolled at least one patient including Colombia (66), Ecuador (35), South Africa (161), US (773).

Primary Objective:
The primary objective was to demonstrate the superior efficacy of the combination of valsartan/amlodipine 160/10 mg and 320/10 mg treatment regimen in Black patients with stage II hypertension, by testing the hypothesis that the valsartan/amlodipine combination treatment regimen produces a superior reduction in mean sitting systolic blood pressure (MSSBP) from baseline compared to amlodipine monotherapy at Week 8.

Secondary objectives:
1. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline MSSBP after 2, 4 and 12 weeks of treatment.
2. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline mean sitting diastolic blood pressure (MSDBP) after 2, 4, 8 and 12 weeks of treatment.
3. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP < 140 mmHg and MSDBP < 90mmHg) after 12 weeks of treatment.
4. To evaluate the safety and tolerability of the valsartan/amlodipine and amlodipine treatment

regimens.

Exploratory objectives:
1. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching diastolic control (defined as MSDBP <90 mmHg) after 2, 4, 8 and 12 weeks of treatment.
2. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP < 140 mmHg and MSDBP < 90mmHg) after 2, 4 and 8 weeks of treatment.
3. To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the incidence and severity of edema.

Study Design:
This was a randomized, double-blind, multinational, two arm, parallel group study. At Visit 2 (Day 1), eligible patients were randomized in a 1:1 ratio to receive valsartan/amlodipine 160/5 mg or amlodipine 5 mg for 2 weeks. At Visit 3 (Week 2), all patients were force titrated to receive an additional 5 mg of amlodipine for 2 weeks. From Visit 3 onwards, patients were treated until the end of the study (Visit 6, Week 12) with either valsartan/amlodipine 160/10 mg or amlodipine 10 mg, unless further optional upward titration was needed.

At Visit 4 (Week 4), patients treated with valsartan/amlodipine 160/10 mg who had not reached the target systolic blood pressure (MSSBP ≥ 130 mmHg) could be up titrated at the investigator's discretion to receive valsartan/amlodipine 320/10 mg, while patients treated with amlodipine 10 mg who had not reached the target systolic blood pressure continued at their current dose (additional placebo to match valsartan 160 mg was administered). At Visit 5 (Week 8), patients in either treatment regimen who had not reached target for systolic blood pressure (<130 mmHg) HCTZ 12.5 mg could be added open label at the discretion of the investigator.

Figure 1 Study Design

<table>
<tr><td>Screening/Washout</td><td colspan="5">Double-blind treatment</td></tr>
<tr><td>(1 week)</td><td colspan="5">(12 weeks)</td></tr>
<tr><td>Visit 1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td></tr>
<tr><td>Days -7 to -3</td><td>Day 1</td><td>Week 2</td><td>Week 4</td><td>Week 8</td><td>Week 12</td></tr>
<tr><td></td><td colspan="5">↓ Randomization</td></tr>
<tr><td rowspan="2"></td><td colspan="4"></td><td>+HCTZ 12.5 mg**</td></tr>
<tr><td colspan="3"></td><td colspan="2">+valsartan/amlodipine 320/10 mg**</td></tr>
<tr><td></td><td></td><td colspan="4">valsartan/amlodipine 160/10 mg*</td></tr>
<tr><td rowspan="2"></td><td colspan="5">valsartan/amlodipine 160/5 mg</td></tr>
<tr><td colspan="5">amlodipine 5 mg</td></tr>
<tr><td></td><td></td><td colspan="4">amlodipine 10 mg*</td></tr>
<tr><td rowspan="2"></td><td colspan="3"></td><td colspan="2">+placebo**</td></tr>
<tr><td colspan="4"></td><td>+HCTZ 12.5 mg**</td></tr>
</table>

* Forced titration
** Optional titration (MSSBP ≥ 130 mmHg)

Main criteria for inclusion:
The study population consisted of Black male and female hypertensive outpatients ≥ 18 years of age with stage II hypertension (MSSBP ≥ 160 mmHg and <200 mmHg).

Table 1 Summary of Eligibility based on medications and Blood Pressure

	Number of Antihypertensive Drugs Being Taken at Visit 1			
BP at Visit 1 MSSBP	0 or 1	2	3	> 3
<140 mmHg	Yes	Yes	Yes	No
≥ 140 and <180 mmHg	Yes	Yes	No	No
≥ 180 mmHg	Yes	No	No	No

Once eligibility was determined, patients entered a 3 to 7 day wash-out period. Patients were instructed to take study medication every morning except on the morning of scheduled study Visits 3, 4, 5 and 6 when study medication was taken at the investigational site after office blood pressure measurements were obtained.

The treatment regimens selected in this study design, 160 mg valsartan / 5 mg amlodipine in combination with a forced titration to 160 mg valsartan / 10 mg amlodipine and later to 320 mg valsartan/10 mg amlodipine (if needed) were chosen.

Table 2 Dosing scheme

Treatment Arm	Visit 2	Visit 3	Visits 4 & 5 MSSBP < 130 mmHg	Visits 4 & 5 MSSBP ≥ 130 mmHg
Val/aml treatment regimen	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg valsartan 160 mg amlodipine 5 mg amlodipine 5 mg HCTZ 12.5 mg*
Amlodipine treatment regimen	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg	valsartan 160 mg placebo valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg HCTZ 12.5 mg*

For both treatment arms the daily dose consisted of one capsule, by mouth, at approximately 8:00 AM from each of 3 or 4 bottles (depending on MSSBP value) containing double blind investigational medication.
* At Visit 5, patients in both treatment arms whose MSSBP was not at systolic target (MSSBP < 130 mmHg) could receive a supplementary dose of open label HCTZ 12.5mg at the investigator's discretion.

Treatment Duration:
The double-blind study medication given to the enrolled patients consisted of valsartan 160 mg capsules (and matching placebo) and amlodipine 5 mg capsules (and matching placebo) for oral administration. Patients who were electively up-titrated to 12.5 mg HCTZ received individual open-label bottles at Visit 5. The duration of the study, including all phases, was 13 weeks. The duration of double-blind treatment was 12 weeks.

Efficacy and safety measurements assessed:
Full details of the assessments are described in the table below.

Table 3 Visit Schedule

Visit	1	2[3]	3	4	5	6
Week	-1 (Day -7/-3)	0 (Day 1)	2	4	8	12
Written informed consent	X					
Demography	X					
Medical history	X					
Inclusion/exclusion criteria	X	X				
Prior/Concomitant medications	X	X	X	X	X	X
Randomization		X				
Dispense home BP measuring device	X					
Dispense study medication		X	X	X	X	
Drug accountability			X	X	X	X
Vital signs and BP measurement	X	X	X	X	X	X
Weight and Height[4]	X					X
Adverse events		X	X	X	X	X
Serious adverse events		X	X	X	X	X
Physical examination	X					
Interim physical examination		X	X	X	X	X
ECG	X					
Hematology	X					X
Blood chemistry	X				X[1]	X
Urinalysis	X					X
Serum Pregnancy test	X					X
Study Completion form[2]						X

1 At visit 5 only Potassium, BUN and creatinine were measured
2 Or at study discontinuation
3 For those patients whose MSSBP was < 160 mmHg after 3 days wash out period, Visit 2 was rescheduled after an additional 4 day washout
4 Height was measured at Visit 1 only

Concomitant medications which were not permitted:
• Drugs approved for the treatment of hypertension even if prescribed for another indication. (Beta-blocker ophthalmic preparations are permitted.)
• Any antidepressant drugs in the MAO inhibitor class, tricyclics and venlafaxine hydrochloride (Effexor®). Other psychotropic drugs such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) were allowed if well tolerated when previously taken and the patient had been on a stable dose for the previous 3 months.
• Chronic use of oral anti-inflammatory steroidal drugs was prohibited. Topical and inhaled steroids and non-steroidal anti-inflammatory drugs (NSAIDS) were allowed. The long-term chronic use of aspirin for pain or cardiac prophylaxis was allowed, provided the total daily dose did not exceed 325 mg. Acetaminophen for chronic or acute pain was allowed.
• Hormonal contraceptives beginning 4 weeks prior to randomization and continuing in trial.
• Thyroid medication and/or estrogen replacement therapy, unless these had been stable maintenance replacement doses for the 6 months preceding Visit 1.
• Chronic administration (defined as > 3 days per week) of sympathomimetic drugs such as those found in nasal decongestants, oral decongestants, diet aids and bronchodilators.
• Antacids in an amount greater than the package labeling.
• Ergot and serotonin (5-hydroxytryptamine) receptor agonist preparations.
• Tamsulosin hydrochloride (Flomax®).
• Sildenafil (Viagra®) and vardenafil (Levitra®) were disallowed within 24 hours prior to any scheduled visit. Tadalafil (Cialis®) was disallowed within 48 hours prior to any scheduled visit.
• Antiarrhythmic drugs, including digoxin.

• Diuretics of any kind (other than study medication).
• Maintenance doses of nitrates were allowed, but if taken 24 hours before visit, visit was rescheduled
• Lithium.
• Opioids and barbiturates.
• Adrenocorticotropic hormone (ACTH).
• Cholestyramine and colestipol resins.
• Oral anticoagulants including warfarin and heparin.
• Drugs approved for the treatment of adult ADHD including Ritalin®, Focalin®, Adderall®, Strattera®, and Concerta®.
• Potent inhibitors of cytochrome P450 3A4 (CYP3A4) including itraconazole, ketoconazole, clarithromycin, erythromycin, nefazodone, and HIV protease inhibitors.

All other non-study medications were allowed provided the need for such medication(s) represented a continuation of a need that existed prior to study entry and remained at stable doses throughout the length of the study. If clinically indicated, a dosage adjustment on a concomitant medication could be made.

Efficacy:
The primary efficacy variable was change from baseline in MSSBP (mmHg) at Week 8 (or LOCF).

Secondary efficacy variables:
Change from baseline MSDBP at Week 8 (or LOCF).
Change from baseline MSSBP and MSDBP at Weeks 2, 4 and 8 and 12.
Overall BP control after 12 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg).

Exploratory efficacy variables:
Overall BP control rate at Weeks 2, 4 and 8 (MSSBP < 140 mmHg and MSDBP < 90 mmHg).
Diastolic BP control rate at Weeks 2, 4, 8 and 12 (MSDBP < 90 mmHg).
Unadjusted systolic BP target rate, systolic BP control rate, diastolic BP control rate and overall BP control rate.

Safety:
Safety assessments consisted of all adverse events (AE) and serious adverse events (SAE), the regular monitoring of hematology and blood chemistry, regular measurement of vital signs, weight and the performance of physical examinations and pregnancy testing. An ECG evaluation and height were conducted at Visit 1.

Statistical methods:
Primary: The primary efficacy variable was analyzed using analysis of covariance (ANCOVA). Treatment, country, length of washout received were fitted as factors in the model and baseline MSSBP as a covariate. The change from baseline LSM, the difference between LS means, (valsartan/amlodipine vs. amlodipine) and two-sided 95% confidence interval were presented.

The null hypothesis would be rejected if the 2-sided p-value < 0.05. For patients who discontinued prior to week 8, the last post-baseline MSSBP measurement collected was carried forward (LOCF). Analysis was performed using the Intent-to-Treat (ITT) population. The primary analysis was repeated using the Per-Protocol population.

Secondary: The change from baseline in MSDBP at Week 8 (or LOCF) and the change from baseline in MSSBP and MSDBP at Visits 3, 4, 5 and 6 (weeks 2, 4, 8 and 12 respectively) was analyzed using the same model as described for the primary analysis.

Patients reaching overall BP control in each treatment regimen at endpoint Visit 6 (week 12) were analyzed using a logistic regression model with treatment and length of washout as fixed factors and baseline MSSBP and baseline MSDBP as covariates. The point estimate for the odds ratio (valsartan/amlodipine vs. amlodipine) and two-sided 95% confidence interval around the odds ratio was presented.

Protocol Amendment and Deviations:
The purpose of Amendment 1 (July 26, 2006), was to clarify for consistency the upper limits of systolic and diastolic blood pressure criteria and the target systolic blood pressure criteria for optional upward titration throughout the protocol, add additional excluded concomitant medications for the treatment of adult ADHD and potent inhibitors of cytochrome P450 3A4 (CYP3A4), and clarify exclusion criteria number 3 which defines the end of the down titration period for those patients who need to taper off of prior antihypertensive medication.

The most frequently reported major deviations were time of BP measurement < 20 or > 30 hours after the last dose of study medication (12.2% for valsartan/amlodipine; 14.7% for amlodipine), study drug interruption > 3 consecutive days prior to Visit 6 (4.2% for valsartan/amlodipine; 5.2% for amlodipine), and MSSBP < 160mmHg or ≥ 200 at Visit 2 (4.2% for valsartan/amlodipine; 3.5% for amlodipine).

No interim analysis was performed.

6.1.3.2 Study CVAA489A 2403

Only important differences from the above study A2402 will be presented here.

Title: An 8-week double-blind, randomized, multicenter, parallel group study to evaluate the efficacy and safety of orally administered valsartan / amlodipine combination based therapy versus amlodipine monotherapy in patients with stage II hypertension

Phase IIIB

Dates: June 9, 2006 to April 10, 2007

Study center(s): A total of 75 centers in 6 countries enrolled at least one patient including US (189), Italy (118), and Mexico

Objectives:
The primary objective was to demonstrate the superior efficacy of the combination of valsartan/amlodipine 160/10 mg in patients with stage II hypertension, by testing the hypothesis that the valsartan/amlodipine 160/10 mg combination regimen produces a superior reduction in MSSBP from baseline compared to amlodipine 10 mg monotherapy at week 4.

Secondary objectives:
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline MSSBP after 2 and 8 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in change from baseline MSDBP after 2, 4 and 8 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP <140 mmHg and MSDBP <90mmHg) after 8 weeks of treatment.
• To evaluate the safety and tolerability of the valsartan/amlodipine and amlodipine treatment regimens.

Exploratory objectives:
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching diastolic control (defined as MSDBP <90 mmHg) after 2, 4 and 8 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the proportion of patients reaching overall BP control (MSSBP <140 mmHg and MSDBP <90mmHg) after 2 and 4 weeks of treatment.
• To compare the valsartan/amlodipine treatment regimen with the amlodipine treatment regimen in the incidence and severity of edema.
• To explore the effect of the valsartan/amlodipine and amlodipine treatment regimens on the 24 hour Ambulatory Blood Pressure Monitoring (ABPM) profiles after 4 weeks of treatment.
• To evaluate mean systolic and diastolic ambulatory blood pressure over 24 hours at week 4
• To evaluate nocturnal and diurnal systolic and diastolic load at week 4
• To explore the effect of the valsartan/amlodipine and amlodipine treatment regimens on non-dipper pattern, where non-dipper is defined as <10 % decline in night-time mean versus the day-time mean of systolic ABPM

Study Design:
This was a randomized, double-blind, multinational, two arm, parallel group study. This study was designed to demonstrate a difference of 3.7 mmHg between treatment arms. The study population consisted of male and female adult outpatients with a documented diagnosis of stage II hypertension, defined as MSSBP of ≥ 160 mmHg and < 200 mmHg. At Visit 2 (day 1), eligible patients were randomized in a 1:1 ratio to receive valsartan/amlodipine 160/5 mg or amlodipine 5 mg for 2 weeks. At Visit 3, all patients were force titrated to receive an additional 5 mg of amlodipine for 2 weeks. From Visit 3 onwards, patients were treated until the end of the study (Visit 5, week 8) with either valsartan/amlodipine 160/10 mg or amlodipine 10 mg, unless the addition of HCTZ was needed to achieve a target MSSBP < 130 mmHg.

Figure 2 Study design

Screening/Washout	Double Blind Treatment			
1- week	8-weeks			
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Day -7 to Day -3	Day 1	Week 2	Week 4	Week 8
	↓ Randomization			
			**+ HCTZ 12.5 mg	
		*valsartan 160 mg / amlodipine 10 mg		
	valsartan 160 mg / amlodipine 5 mg			
	amlodipine 5 mg			
		*amlodipine 10 mg		
			**+ HCTZ 12.5 mg	

* Forced titration
** Optional titration (MSSBP ≥ 130 mmHg

Main criteria for inclusion:
The study population consisted of male and female hypertensive outpatients ≥ 18 years of age with stage II hypertension (MSSBP ≥ 160 mmHg and < 200 mmHg). Patients with a systolic blood pressure ≥ 200 mmHg and/or a diastolic blood pressure ≥ 120 mmHg did not meet inclusion criteria.

Table 4 Summary of eligibility

	Number of Antihypertensive Drugs Being Taken at Visit 1			
BP at Visit 1 MSSBP	0 or 1	2	3	> 3
< 140 mmHg	Yes	Yes	Yes	No
≥ 140 and < 180 mmHg	Yes	Yes	No	No
≥ 180 mmHg	Yes	No	No	No

Once eligibility was determined, laboratory samples were collected for evaluation, and patients taking antihypertensive medication entered a 3 to 7 day washout period.

Duration of treatment:
The duration of the study, including all phases, was 9 weeks. The duration of double-blind treatment was 8 weeks.

Treatments:
At Visit 1 (screening), patients meeting eligibility criteria were directed to discontinue their antihypertensive medication for a 3 to 7 day washout period. At Visit 2, eligible patients were assigned to either combination therapy with valsartan/amlodipine 160/5 mg or amlodipine 5 mg monotherapy in a ratio of 1:1. Patients in both groups took 3 capsules/day for 2 weeks (valsartan 160 mg + amlodipine 5 mg + placebo matching amlodipine 5 mg OR amlodipine 5 mg plus 2 placebo capsules to match amlodipine and valsartan).

At Visit 3, all patients were force titrated to receive an additional 5 mg of amlodipine for 2 weeks. From this point forward, patients were treated until the end of the study (Visit 5, week 8) with either valsartan/amlodipine 160/10 mg or amlodipine 10 mg. At Visit 4, if the patient had not reached target systolic blood pressure (MSSBP < 130 mmHg), 12.5 mg HCTZ open label

medication could be added to the previous treatment regimen at the discretion of the investigator. HCTZ was not to be added if the patient had reached target systolic blood pressure.

Table 5 Dosing scheme

Treatment Arm	Visit 2	Visits 3 & 4
valsartan/amlodipine treatment regimen	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg amlodipine 5 mg amlodipine 5 mg
amlodipine treatment regimen	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg placebo	valsartan 160 mg placebo amlodipine 5 mg amlodipine 5 mg
For both treatment arms the daily dose consisted of one capsule, by mouth, at approximately 8:00 AM from each of 3 bottles containing double blind investigational medication. Patients who received open label HCTZ took 4 capsules/day (3 capsules double-blind + one capsule open label).		

Efficacy and Safety Assessment Schedule:

Table 6 Assessment schedule

Visit	1	2[4]	3	4	5
Week	-1 (day -7/-3)	0 (day 1)	2	4	8
Written informed consent	X				
Demography	X				
Medical history	X				
Inclusion/exclusion criteria	X	X			
Prior/Concomitant medications	X	X	X	X	X
Randomization		X			
Dispense home BP measuring device	X				
Dispense study medication[5]		X	X	X	
Drug accountability			X	X	X
Vital signs and BP measurement	X	X	X	X	X
ABPM[1]		X		X	
Adverse events		X	X	X	X
Serious adverse events		X	X	X	X
Physical examination	X				
Interim physical examination		X	X	X	X
ECG	X				
Hematology	X				X
Blood chemistry	X			X[2]	X
Serum Pregnancy test	X				X
Study Completion Form[3]					X

[1] For ABPM sub-study participants only (approx. 100 patients in selected centers)
[2] Only potassium, BUN and creatinine were measured at Visit 4
[3] Or at study discontinuation
[4] For patients with MSSBP < 160 mmHg after 3 day washout period Visit 2 was rescheduled after an additional 4 day washout
[5] ABPM sub-study patients were dispensed study medication according to Table 9-5

Table 7 24-hour ABPM Schedule

Visit	2	24-hours after V2	4	24-hours after V4
Week	Day 1		4	
Perform visit assessments	X		X	
Record BP and pulse before application of ABPM device	X		X	
Apply ABPM device	X		X	
Perform correlation	X		X	
Verify success criteria		X		X
Remove ABPM		X		X
Dispense study medication		X	X	X[1]
1 – HCTZ, if indicated, was dispensed 24 hours after V4.				

Office blood pressure measurements were made using an Omron blood pressure monitor in accordance with the Guidelines for Management of Hypertension, British Hypertension Society 2004, at trough (24 hours ± 3 hours post-dose), i.e. just prior to taking the morning dose of medication. The same arm was used at all visits. Ideally, the same clinician obtained blood pressure measurements for the same patients at each visit, using the same equipment.

Sitting and standing blood pressure were measured at each visit. After the patient had been sitting for 5 minutes, blood pressure was measured three times at 2 to 3 minute intervals. The mean of the three sitting blood pressure measurements was used as the average of sitting office blood pressure at each visit. Standing BP was measured only once, within 2 minutes after the last sitting BP measurement.

Self measured blood pressure (SMBP) was included in the study design to aid patients and investigators in identifying potentially emergent hypertensive situations that may have occurred during prior antihypertensive washout and throughout the course of the trial. SMBP information was not recorded for analysis.

Ambulatory Blood Pressure Monitoring (ABPM) was conducted over a 24-hour period at two time points during the study, V2 and V4. Following office blood pressure measurements, the ABPM device was applied. The device was pre-set to collect readings every 15 minutes during the day (6AM to 10PM) and every 30 minutes during the night (10PM to 6AM). Patients were asked to return to the site the following day (25-26 hours after the start of ABPM) to remove the ABPM device. At Visit 2 patients in the ABPM sub-study received their first dose of double-blind medication upon removal of the ABPM device, 25-26 hours after Visit 2. Mean hourly systolic and diastolic blood pressure were calculated for each patient at post dosing hours 1-24. Each patient's post-dosing hours (1-24) was determined relative to that patient's dosing time. Only valid ABPM measurements made at or within 24 hours of the dosing time were used in this calculation.

All available values at a certain "post-dosing" hour were weighted equally to obtain the mean systolic and diastolic values for that "post-dosing" hour. The mean systolic and diastolic ambulatory blood pressure over 24 hours for a patient were calculated by averaging the patient's available hourly means (assigning equal weight to the available hourly means) for post dosing hours 1-24. All other evaluation of ABPM was done centrally and instructions for transmitting the data were provided. ABPM readings remained blinded to patients, investigators and study site personnel.

Efficacy:
The primary efficacy variable was the change from baseline in mean sitting systolic blood pressure (MSSBP) LOCF Week 4. LOCF Week 4 was defined as the week 4 value or last non-missing post-dose value (last observation carried forward). The parameter was in the protocol named as Endpoint (Week 4).

Secondary efficacy variables:

Change from baseline MSDBP at Week 4 (last observation carried forward; LOCF)
Change from baseline MSSBP and MSDBP at Weeks 2, 4 and 8
Overall BP control rate after 8 weeks of treatment (MSSBP <140 mmHg and MSDBP <90 mmHg)

Exploratory efficacy variables:
Overall BP control rate at Weeks 2 and 4 (MSSBP < 140 mmHg and MSDBP < 90 mmHg)
Diastolic BP control rate at Weeks 2, 4 and 8 (MSDBP < 90 mmHg)
Unadjusted systolic BP target rate, systolic BP control rate, diastolic BP control rate and overall BP control rate

Safety:
Safety assessments consisted of all adverse events (AE) and serious adverse events (SAE), hematology and blood chemistry, measurement of vital signs and the performance of physical examinations and pregnancy testing. An ECG evaluation was conducted at Visit 1.

Statistical methods:
The primary efficacy variable was the change from baseline in MSSBP (mmHg) at LOCF Week 4. The change from baseline in MSSBP LOCF Week 4 was analyzed using analysis of covariance (ANCOVA). Treatment, country and length of washout were fitted as factors and baseline MSSBP as a covariate. The least square means, treatment difference with 95% confidence interval, and p-value were presented.

The primary and secondary analyses were performed using the ITT population. The secondary variables, change from baseline MSSBP and MSDBP were analyzed separately for weeks 2, 4, week 4 LOCF (MSDBP only) and 8 with the same model as described for MSSBP in the primary analysis. In addition, MSSBP and MSDBP were summarized using descriptive statistics by treatment strategy and time point (Week 2, Week 4, pre-HCTZ LOCF Week 4 and Week 8). Subgroup analysis for severity of hypertension at baseline, diabetic status, age group, sex and race were performed.

The number of patients with overall BP control (MSSBP < 140 mmHg and MSDBP < 90 mmHg) at Week 8 was analyzed using a logistic regression model with treatment and length of wash-out as fixed factors, baseline MSSBP and baseline MSDBP as covariates.

The change from baseline in mean ambulatory blood pressure monitoring (ABPM) over 24 hours (systolic and diastolic), the change from baseline in daytime/nighttime (systolic and diastolic) was analyzed using an ANCOVA model with treatment, country, length of wash-out as factors and baseline variable as a covariate. To estimate hourly changes from baseline to assess intra-dosing effects, a repeated-measures ANCOVA with treatment, country, length of wash-out, post-dosing hours (hour 0,1, 2, 3, …, or 23) as factors and baseline mean 24-hour MASBP as a covariate was applied. Treatment by post-dosing-hour interaction was included in the model. All analyses for ABPM were carried out using the ABPM population.

Summary statistics for systolic diurnal load (the proportion of SBP readings >135 mmHg), the diastolic diurnal load (the proportion of DBP readings >85 mmHg), the systolic nocturnal load (the proportion of SBP readings >120 mmHg) and the diastolic nocturnal load (the proportion of DBP readings >70 mmHg) were presented by visit and treatment group. Summary statistics for Smoothness Index by each treatment group was calculated.

The rate of patients experiencing edema was compared using logistic regression with treatment, sex, race and age category (<65, ≥ 65 yrs) as factors. The same analysis was repeated for peripheral edema.

Protocol Amendment and Deviations:
The purpose of Amendment 1 (July 14, 2006), was to clarify for consistency the upper limits of systolic and diastolic blood pressure criteria throughout the protocol, add additional excluded concomitant medications for the treatment of adult ADHD and potent inhibitors of cytochrome P450 3A4 (CYP3A4), and clarify exclusion criteria number 3 which defined the end of the down-titration period for those patients who needed to taper off of prior antihypertensive medication.

Table 8 Patient disposition - Randomized population

Disposition Reason	Val/Aml N=322 n (%)	Amlodipine N=324 n (%)	Total N=646 n (%)
Completed	289 (89.8)	288 (88.9)	577 (89.3)
Discontinuations	33 (10.2)	36 (11.1)	69 (10.7)
Adverse event(s)	19 (5.9)	19 (5.9)	38 (5.9)
Subject withdrew consent	7 (2.2)	15 (4.6)	22 (3.4)
Lost to follow-up	3 (0.9)	1 (0.3)	4 (0.6)
Administrative problems	1 (0.3)	1 (0.3)	2 (0.3)
Abnormal test procedure result(s)	2 (0.6)	0 (0.0)	2 (0.3)
Protocol deviation(s)	1 (0.3)	0 (0.0)	1 (0.2)

Protocol deviations occurred in 92 patients (28.6%) in the valsartan/amlodipine treatment strategy, and in 87 patients (26.9%) in the amlodipine treatment strategy. Approximately half were major deviations (46 /14.3% for valsartan/amlodipine; 47 / 14.5% for amlodipine). The most frequently reported major deviations were time of BP measurement < 20 hours before or > 30 hours after the last dose of study medication (23 / 7.1% for valsartan/amlodipine; 26 /8.0% for amlodipine) and patients with a visit 1 MSSBP ≥ 140 mmHg and <180 mmHg.

6.1.4 Efficacy Findings

6.1.4.1 Study CVAA489A 2402

Efficacy assessments:
The following populations were used in the analysis:
Randomized population (RAN): All patients who had received a randomization number, regardless of study medication intake. ITT population (ITT): All patients as randomized who had a baseline and at least one postbaseline efficacy assessment. Following the intent-to-treat

principle, patients were analyzed according to the treatment they were assigned to at randomization.

Safety population (SAF): All patients who received at least one dose of double-blind study drug. Patients were analyzed according to treatment received.

Per-Protocol population (PP): All ITT patients who completed the trial without any major deviations from the protocol procedures in a manner liable to affect the efficacy assessment. Protocol deviations that would exclude a patient from the per-protocol population were prespecified prior to unblinding the treatment codes for analyses. The supplemental efficacy population is the PP population. It was used to assess robustness of the primary efficacy analysis results from the ITT population.

Study Medication:
The duration (Weeks) of the randomized trial medication was summarized for the Safety population by treatment strategy. Study drug interruptions were not accounted while calculating treatment duration since they were not captured on the CRFs.

The following algorithm was used to calculate the treatment duration:
If the last date the patient took study drug was known, treatment duration was calculated as:
Treatment duration (Weeks) = (last study drug date – randomization date + 1)/7.

If the last date the patient took study drug was unknown or missing, the last visit date was substituted: Treatment duration (Weeks) = (last visit date – randomization date + 1)/7.

If the last date the patient took study drug was incomplete:
• Treatment duration (days) was determined using Novartis standard convention – when calculating relative days, partial dates with missing day only will assumed to be 15th of the month, and partial dates with both missing day and month was assumed to be July 1.
• If the imputed date is beyond the last visit date then the last visit date was used instead.
• If the imputed date is before treatment start date then last date was treatment start date+1.

Summary statistics (mean, SD, median, minimum, maximum) of the duration exposure (Weeks) to study medication, regardless of dose levels, were presented by treatment strategy. Frequency counts by following exposure categories were presented:
0 - <2 Weeks
2 - <4 Weeks
4 - <8 Weeks
8 - ≤ 12 Weeks
Actual durations of greater than 12 Weeks were included in the "8 - <=12 Weeks" category.

Frequency counts and percentages were also presented in the following four categories,
• No up titration, no HCTZ intake
• Up titration but no HCTZ intake
• No up titration but HCTZ intake

• Both up titration and HCTZ intake
for the combined HCTZ intake and the up titration of valsartan/amlodipine 320/10 mg separately for both treatment strategies.

Concomitant medications as well as significant non-drug therapies were summarized by treatment strategy for the Safety population. Concomitant medications and significant nondrug therapies were defined as any medication or significant non-drug therapies taken on or after visit 2, which also included medications and significant non-drug therapies that were ongoing at the start of Visit 2.

Due to a data programming issue, prior and concomitant medications could not be separated. This had a minor implication on the reporting of the data. Prior and concomitant medications were therefore summarized in one table.

Patients were assigned into the category of length of wash-out as follows:
• A patient with no prior antihypertensive medication recorded within the last 3 months before visit 1 was assigned to the **naïve group** (based on no entry for prior antihypertensive medication or the end date of the antihypertensive medication > 90 days in comparison to the visit 1 date).
• If the antihypertensive end date was not missing, a patient who had not stopped the antihypertensive medication more than 90 days before visit 1 was assigned to either the **3 day washout category** (actual washout of 0-4 days) or the **7 day wash-out category** (actual washout of ≥ 5 days) depending on his actual number of wash-out days. The actual number of wash-out days was calculated as Visit 2 date - End date of the antihypertensive medication -1.

• If the antihypertensive medication end date was missing, the following rules were applied:
1. If the day of month was missing, it was set to either the last day of the month or the date of Visit 1, if Visit 1 occurred earlier than the end of the month.
2. If the month was missing, the date was set to the end of the year or the date of Visit 1 if Visit 1 occurred earlier than the end of the year.

If the antihypertensive medication end date was missing and there was any indication that the patient had taken antihypertensive medication within the past 3 months prior to Visit 1, the length of wash-out was set to missing.

Severity of hypertension at baseline (Visit 2):
1. Baseline MSSBP < 180 mmHg
2. Baseline MSSBP ≥ 180 mmHg

Diabetic status (2 levels):
1. Yes = the patient has controlled type 2 diabetes mellitus
2. No = the patient does not have type 2 diabetes mellitus

Age group (2 levels):
1. age < 65
2. age ≥ 65

Patient Disposition:

Table 9 Disposition of Patients

Disposition Reason	Val/Aml N=286 n (%)	Amlodipine N=286 n (%)	Total N=572 n (%)
Screened			1042
Completed	247 (86.4)	250 (87.4)	497 (86.9)
Discontinued	39 (13.6)	36 (12.6)	75 (13.1)
Lost to follow-up	13 (4.5)	5 (1.7)	18 (3.1)
Subject withdrew consent	9 (3.1)	8 (2.8)	17 (3.0)
Adverse event(s)	7 (2.4)	9 (3.1)	16 (2.8)
Protocol deviation	8 (2.8)	7 (2.4)	15 (2.6)
Administrative problems	2 (0.7)	2 (0.7)	4 (0.7)
Abnormal test procedure result(s)	0 (0.0)	2 (0.7)	2 (0.3)
Unsatisfactory therapeutic effect	0 (0.0)	2 (0.7)	2 (0.3)
Abnormal laboratory value(s)	0 (0.0)	1 (0.3)	1 (0.2)

Demographic and Baseline Characteristics:

Table 10 Demographics by treatment strategy in Randomized population

Demographic variable	Val/Aml N=286	Amlodipine N=286	Total N=572
Age (years)			
n	286	286	572
Mean (SD)	52.9 (10.18)	53.6 (11.79)	53.2 (11.01)
Range	22-81	22-87	22-87
Age Group (years)			
< 65	244 (85.3%)	231 (80.8%)	475 (83.0%)
≥ 65	42 (14.7%)	55 (19.2%)	97 (17.0%)
< 70	265 (92.7%)	253 (88.5%)	518 (90.6%)
≥ 70	21 (7.3%)	33 (11.5%)	54 (9.4%)
< 75	279 (97.6%)	270 (94.4%)	549 (96.0%)
≥ 75	7 (2.4%)	16 (5.6%)	23 (4.0%)
Gender			
Male	120 (42.0%)	108 (37.8%)	228 (39.9%)
Female	166 (58.0%)	178 (62.2%)	344 (60.1%)
Race			
Black	286 (100%)	286 (100%)	572 (100%)
Ethnicity			
Hispanic/Latino	46 (16.1%)	49 (17.1%)	95 (16.6%)
Other	237 (82.9%)	236 (82.5%)	473 (82.7%)
Mixed Ethnicity	1 (0.3%)	0 (0.0%)	1 (0.2%)
Height (cm)			
n	286	286	572
Mean (SD)	166.7 (9.87)	167.4 (9.89)	167.0 (9.88)
Range	142-198	142-201	142-201
Weight (kg)			
n	285	284	569
Mean (SD)	89.3 (20.94)	91.1 (21.73)	90.2 (21.34)
Range	50-175	55-195	50-195
BMI (kg/m2)			
n	285	284	569
Mean (SD)	32.1 (6.66)	32.5 (7.23)	32.3 (6.95)
Range	18-55	19-73	18-73

Table 11 Baseline characteristics by treatment strategy in Randomized population

Parameter	Val/Aml N=286	Amlodipine N=286	Total N=572
MSSBP (mmHg)			
N	286	285	571
Mean (SD)	170.4 (9.62)	170.5 (8.92)	170.5 (9.27)
Range	116-199	150-198	116-199
MSDBP (mmHg)			
N	286	285	571
Mean (SD)	98.5 (10.94)	98.2 (10.14)	98.3 (10.54)
Range	69- 120	76- 129	69-129
Sitting pulse (bpm)			
N	286	285	571
Mean (SD)	76.5 (12.81)	77.7 (13.06)	77.1 (12.94)
Range	40-125	48-116	40-125
Standing SBP (mmHg)			
N	284	279	563
Mean (SD)	169.5 (15.11)	169.5 (13.76)	169.5 (14.44)
Range	106-208	113-212	106-212
Standing DBP (mmHg)			
N	284	279	563
Mean (SD)	102.1 (12.61)	102.6 (11.40)	102.3 (12.02)
Range	68-134	76-134	68-134
Standing pulse (bpm)			
N	284	279	563
Mean (SD)	80.1 (13.92)	82.5 (14.34)	81.3 (14.17)
Range	47-172	49-169	47-172
Length of washout category			
Treatment naive	51 (17.8%)	56 (19.6%)	107 (18.7%)
3 days (0-4 days)	118 (41.3%)	128 (44.8%)	246 (43.0%)
7 days (≥ 5 days)	117 (40.9%)	102 (35.7%)	219 (38.3%)
Diabetes status			
No	239 (83.6%)	245 (85.7%)	484 (84.6%)
Yes	47 (16.4%)	41 (14.3%)	88 (15.4%)
Hypertension severity at baseline			
MSSBP < 180 mmHg	247 (86.4%)	243 (85.0%)	490 (85.7%)
MSSBP ≥ 180 mmHg	39 (13.6%)	42 (14.7%)	81 (14.2%)

Primary efficacy results:
The primary efficacy variable was the change from baseline to Week 8 in MSSBP. The adjusted least square mean change was -33.3 mmHg in the valsartan/amlodipine regimen and -26.6 mmHg in the amlodipine regimen. The difference in the reduction was statistically significant ($p<0.0001$). Similar reductions were achieved in the Per Protocol population.

Table 12 Change from baseline in MSSBP (mmHg) at Week 8 (LOCF) by treatment strategy (Intent-to-treat population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=278)	277	170.5	-33.3 (1.20)	-6.6	(-9.12, -4.11)	<.0001*
Amlodipine (N=278)	278	170.6	-26.6 (1.18)			

N is the number of patients in the ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 8 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine.
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Table 13 Supportive analysis of the primary efficacy variable: Change from baseline in MSSBP at Week 8 (LOCF) by treatment strategy (Per protocol population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=211)	211	171.3	-33.7 (1.37)	-6.4	(-9.25, -3.50)	<.0001*
Amlodipine (N=205)	205	171.3	-27.3 (1.37)			

N is the number of patients in PP population; n is the number of PP patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 8 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine.
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Secondary efficacy results for MSDBP and MSSBP are not included in this review.

Reviewer's comment:
The FDA statistical reviewer also conducted a sub-group analysis by region. The result showed patients who received valsartan/amlodipine exhibited greater reduction in change from baseline in MSSBP at week 8 than did those who received amlodipine in both U.S and non-US populations.

Sub-group Analysis by Region

Region	Treatment	N	Baseline Mean	LSM Change from Baseline	Difference	95% CI
US	Val/Aml	194	170.75	-28.76	-6.06	-9.21, -2.91
	Amlodipine	193	170.40	-22.70		
Non-Us	Val/Aml	83	170.06	-36.21	-8.1	-12.20, -4.14
	Amlodipine	85	171.01	-28.05		

Exploratory analysis results:
Overall blood pressure control was defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg. At Week 8 (LOCF), there were significantly greater proportions of patients who achieved overall blood pressure control in the valsartan/amlodipine group than in the amlodipine group (48.4% vs. 29.5%). This was also true at Weeks 2, 4, 8 and 12.

Table 14 Proportion of unadjusted overall BP control by week and treatment ITT

Timepoint	Treatment	n	No. (%) of BP controlled [1]	95% CI*
Week 2	Val/Aml (N=278)	277	78 (28.2)	(22.86, 33.46)
	Amlodipine (N=278)	278	51 (18.3)	(13.80, 22.90)
Week 4	Val/Aml (N=278)	267	115 (43.1)	(37.13, 49.01)
	Amlodipine (N=278)	269	82 (30.5)	(24.98, 35.98)
Week 8	Val/Aml (N=278)	257	128 (49.8)	(43.69, 55.92)
	Amlodipine (N=278)	265	80 (30.2)	(24.66, 35.72)
Week 12	Val/Aml (N=278)	250	143 (57.2)	(51.07, 63.33)
	Amlodipine (N=278)	251	90 (35.9)	(29.92, 41.79)

Week 8^ is Week 8 or the last observation carried forward value.
N is the number of patients in ITT population; n is the number of ITT patients with a non-missing measurement at that timepoint.

[1] overall BP control defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg.
* The asymptotic confidence intervals are presented.

Systolic BP control was defined as MSSBP <140 mmHg. Compared to those who received amlodipine, larger proportions of patients who received valsartan/amlodipine achieved systolic BP control during the double-blind period: 33.6% vs. 23.4% at Week 2; 49.8% vs. 36.4% at Week 4, 58.0% vs. 37.0% at Week 8, 56.3% vs. 36.3% at Week 8 (LOCF) and 62.4% vs. 47.0% at Week 12. The confidence intervals either did not overlap [Weeks 4, 8, 8 (LOCF) and 12], or overlapped only slightly (Week 2).

Diastolic BP control was defined as MSDBP <90 mmHg. Compared to amlodipine, significantly greater numbers and proportions of patients receiving valsartan/amlodipine achieved diastolic BP control at each assessment during the double-blind period (54.9% vs. 44.2% at Week 2; 67.0% vs. 56.5% at Week 4; 70.0% vs. 57.4% at Week 8, 69.3% vs. 55.8% at Week 8 (LOCF) and 74.4% vs. 61.0% at Week 12.

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Patient Disposition:
Table 15 Number (%) of patients in analysis populations by treatment strategy

Population	Val/Aml n (%)	Amlodipine n (%)	Total n (%)
Screened			957
Randomized	322 (100.0)	324 (100.0)	646 (100.0)
Intent-to-treat	318 (98.8)	321 (99.1)	639 (98.9)
Safety	321 (99.7)	323 (99.7)	644 (99.7)
Per-protocol	272 (84.5)	275 (84.9)	547 (84.7)
ABPM	43 (13.4)	33 (10.2)	76 (11.8)

Demographic and Baseline Characteristics:

Table 16 Demographics by treatment strategy

Demographic Variable	Val/Aml 160/10mg N=322	Amlodipine 10mg N=324	Total N=646
Age (years)			
n	322	324	646
Mean (SD)	58.1 (10.24)	58.1 (10.44)	58.1 (10.33)
Range	32-84	28-89	28-89
Age Groups (years)			
<65	235 (73.0%)	234 (72.2%)	469 (72.6%)
≥ 65	87 (27.0%)	90 (27.8%)	177 (27.4%)
<70	274 (85.1%)	282 (87.0%)	556 (86.1%)
≥ 70	48 (14.9%)	42 (13.0%)	90 (13.9%)
<75	303 (94.1%)	303 (93.5%)	606 (93.8%)
≥ 75	19 (5.9%)	21 (6.5%)	40 (6.2%)
Gender			
Male	165 (51.2%)	159 (49.1%)	324 (50.2%)
Female	157 (48.8%)	165 (50.9%)	322 (49.8%)
Race			
Caucasian	261 (81.1%)	267 (82.4%)	528 (81.7%)
Other	23 (7.1%)	23 (7.1%)	46 (7.1%)
Asian	16 (5.0%)	21 (6.5%)	37 (5.7%)
Black	21 (6.5%)	12 (3.7%)	33 (5.1%)
Native American	1 (0.3%)	0 (0.0%)	1 (0.2%)
Pacific islander	0 (0.0%)	1 (0.3%)	1 (0.2%)
Ethnicity			
Other	206 (64.0%)	209 (64.5%)	415 (64.2%)
Hispanic/Latino	113 (35.1%)	111 (34.3%)	224 (34.7%)
Indian (Indian subcont.)	2 (0.6%)	3 (0.9%)	5 (0.8%)
Chinese	1 (0.3%)	0 (0.0%)	1 (0.2%)
Mixed ethnicity	0 (0.0%)	1 (0.3%)	1 (0.2%)
Height (cm)			
n	322	323	645
Mean (SD)	166.4 (10.41)	166.3 (9.67)	166.4 (10.04)
Range	142-196	140-198	140-198
Weight (kg)			
n	322	323	645
Mean (SD)	82.8 (17.50)	84.2 (19.41)	83.5 (18.48)
Range	50-146	40-191	40-191
BMI (kg/m2)			
n	322	323	645
Mean (SD)	29.8 (5.42)	30.3 (5.70)	30.1 (5.56)
Range	18-52	17-55	17-55

Table 17 Baseline disease characteristics by treatment strategy

Parameter	Val/Aml 160/10mg N=322	Amlodipine 10mg N=324	Total N=646
MSSBP (mmHg)			
n	322	324	646
Mean (SD)	170.2 (8.92)	170.9 (8.52)	170.5 (8.72)
Range	154-198	148-197	148-198
MSDBP (mmHg)			
n	322	324	646
Mean (SD)	95.6 (9.88)	94.7 (10.47)	95.2 (10.18)
Range	65-120	65-119	65-120
Sitting pulse (bpm)			
n	322	323	645
Mean (SD)	75.4 (12.16)	74.8 (12.03)	75.1 (12.08)
Range	46-130	43-110	43-130
Standing SBP (mmHg)			
n	313	320	633
Mean (SD)	166.8 (13.38)	166.2 (12.93)	166.5 (13.14)
Range	131-214	131-204	131-214
Standing DBP (mmHg)			
n	313	320	633
Mean (SD)	97.7 (11.46)	97.2 (11.23)	97.4 (11.34)
Range	63-132	57-124	57-132
Standing pulse(bpm)			
n	313	317	630
Mean (SD)	78.1 (12.65)	77.4 (12.36)	77.7 (12.50)
Range	48-132	46-124	46-132
Length of washout category (number of days)			
0 (naïve)	73 (22.7%)	57 (17.6%)	130 (20.1%)
3 (0-4 days)	161 (50.0%)	180 (55.6%)	341 (52.8%)
7 (≥ 5 days)	88 (27.3%)	87 (26.9%)	175 (27.1%)
Diabetes status			
No	287 (89.1%)	288 (88.9%)	575 (89.0%)
Yes	35 (10.9%)	36 (11.1%)	71 (11.0%)
ABPM participant			
No	271 (84.2%)	283 (87.3%)	554 (85.8%)
Yes	51 (15.8%)	41 (12.7%)	92 (14.2%)
Hypertension severity at baseline			
MSSBP < 180 mmHg	275 (85.4%)	268 (82.7%)	543 (84.1%)
MSSBP ≥ 180 mmHg	47 (14.6%)	56 (17.3%)	103 (15.9%)

Most patients had at least one past or continuing medical condition (74.2% for valsartan/amlodipine; 75.0% for amlodipine), which occurred at generally similar frequencies in both treatment strategies. The most frequently reported conditions (i.e., those reported for at least 15% of the patients in either treatment strategy) were metabolism and nutrition disorders (41.3% for valsartan/amlodipine; 42.6% for amlodipine), musculoskeletal and connective tissue disorders (28.6% for valsartan/amlodipine; 24.4% for amlodipine), surgical and medical procedures (21.4% for valsartan/amlodipine; 22.2% for amlodipine), gastrointestinal disorders (18.0% for valsartan/amlodipine; 17.9% for amlodipine), and nervous system disorders (16.5% for valsartan/amlodipine; 9.6% for amlodipine).

Primary efficacy results:
The primary efficacy variable was the change from baseline in MSSBP (mmHg) at Week 4. Patients who received valsartan/amlodipine exhibited significantly greater LSM reductions from baseline in MSSBP at Week 4 than did those who received amlodipine (30.1 mmHg and 23.5 mmHg, respectively). The difference in the reduction was statistically significant ($p < 0.0001$).

Table 18 Primary efficacy analysis: Change from baseline in MSSBP (mmHg) at Week 4 (LOCF) by treatment strategy (ITT population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=318)	318	170.2	-30.1 (0.79)	-6.6	(-8.59, -4.56)	<.0001*
Amlodipine (N=321)	321	170.8	-23.5 (0.81)			

N is the number of patients in the ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Table 19 Supportive primary efficacy analysis: Change from baseline in MSSBP (mmHg) at Week 4 (LOCF) by treatment strategy (Per-protocol population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=272)	272	170.3	-30.2 (0.84)	-6.3	(-8.38, -4.14)	<.0001*
Amlodipine (N=275)	275	170.7	-23.9 (0.85)			

N is the number of patients in per-protocol population; n is the number of per-protocol patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is val/aml minus amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Secondary efficacy results:
Patients who received valsartan/amlodipine exhibited significantly greater LSM reductions from baseline in MSDBP at Week 4 (LOCF) than did those who received amlodipine (12.5 mmHg and 8.6 mmHg, respectively; p <0.0001).

Table 20 Change from baseline in MSDBP (mmHg) at Week 4 (LOCF) by treatment strategy (ITT population)

Treatment	n	Baseline mean	LSM change (SEM)	Difference[1]	95% CI	p-value
Val/Aml (N=318)	318	95.7	-12.5 (0.44)	-3.9	(-5.05, -2.78)	<.0001*
Amlodipine (N=321)	321	94.7	-8.6 (0.45)			

N is the number of patients in ITT population; n is the number of ITT patients with both baseline and endpoint non-missing values.
LOCF is the value at Week 4 or the last observation carried forward value
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is Val/Aml minus Amlodipine
ANCOVA model with treatment strategy, country and length of washout as factors and baseline MSDBP as covariate.
* p-value < 0.05

Additional analyses of MSSBP and MSDBP by week also showed significantly greater

reductions (p <0.0001) with valsartan/amlodipine than with amlodipine at each week of the double-blind period for both parameters. In both treatment strategies, the greatest reductions were achieved at Week 8.

Table 21 Change from baseline in MSDBP by week and treatment strategy (ITT population)

Timepoint	Treatment strategy	n	Baseline mean	LSM change (SEM)	Difference [1]	95% CI	p-value
Week 2	Val/Aml (N=318)	317	95.6	-9.0 (0.45)	-3.3	(-4.41, -2.12)	<.0001*
	Amlodipine (N=321)	320	94.6	-5.8 (0.46)			
Week 4	Val/Aml (N=318)	307	95.7	-12.9 (0.43)	-4.2	(-5.32, -3.10)	<.0001*
	Amlodipine (N=321)	307	94.9	-8.7 (0.45)			
Week 8	Val/Aml (N=318)	296	95.9	-13.9 (0.45)	-4.5	(-5.60, -3.32)	<.0001*
	Amlodipine (N=321)	299	94.8	-9.4 (0.45)			

N is the number of patients in the ITT population; n is the number of ITT patients with baseline and post-baseline non-missing values.
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is Val/Aml minus Amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSDBP as covariate.
* p-value < 0.05

Table 22 Change from baseline in MSSBP (mmHg) by week and treatment strategy (ITT population)

Timepoint	Treatment strategy	n	Baseline mean	LSM change (SEM)	Difference [1]	95% CI	p-value
Week 2	Val/Aml (N=318)	317	170.2	-23.3 (0.84)	-4.7	(-6.84, -2.57)	<.0001*
	Amlodipine (N=321)	320	170.8	-18.6 (0.86)			
Week 4	Val/Aml (N=318)	307	170.2	-30.7 (0.76)	-7.1	(-8.99, -5.13)	<.0001*
	Amlodipine (N=321)	307	170.8	-23.6 (0.78)			
Week 8	Val/Aml (N=318)	296	170.2	-32.0 (0.78)	-5.6	(-7.61, -3.63)	<.0001*
	Amlodipine (N=321)	299	170.7	-26.4 (0.79)			

N is the number of patients in ITT population; n is the number of ITT patients with baseline and post-baseline non-missing values.
LSM change = least squares mean change from baseline, SEM = standard error of the mean
[1] Difference is Val/Aml minus Amlodipine
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP as covariate.
* p-value < 0.05

Sub-group analysis results:
As in the overall ITT population, subgroup analyses of the change from baseline in BP by severity of hypertension showed valsartan/amlodipine to be significantly more effective than amlodipine in reducing MSSBP and MSDBP at Week 4 of the double-blind period in patients with baseline MSSBP <180 mmHg. Similar results were shown in patients with baseline MSSBP ≥ 180 mmHg.

Table 23 Subgroup analysis: Change from baseline in MSSBP and MSDBP (mmHg) at Week 4 by treatment strategy and severity of hypertension at baseline (ITT population)

	MSSBP < 180 at baseline		MSSBP ≥ 180 at baseline	
	Val/Aml 160/10 mg	Amlodipine 10 mg	Val/Aml 160/10 mg	Amlodipine 10 mg
Statistic	N=272	N=266	N=46	N=55
MSSBP				
LSM change (SEM)	-28.7 (0.84)	-22.1 (0.87)	-40.1 (1.92)	-31.7 (1.94)
Difference [1]	-6.60		-8.42	
95% CI	(-8.71, -4.49)		(-13.62, -3.22)	
p-value	<.0001*		0.0018*	
MSDBP				
LSM change (SEM)	-12.4 (0.49)	-8.0 (0.51)	-14.6 (0.99)	-12.2 (1.01)
Difference [1]	-4.46		-2.47	
95% CI	(-5.70, -3.23)		(-5.11, 0.17)	
p-value	<.0001*		0.0667	

N is the number of patients in the ITT population.
LSM change = least squares mean change from baseline, SEM = standard error of the mean.
[1] Difference is Val/Aml 160/10 mg minus Amlodipine 10 mg.
ANCOVA model with treatment, country and length of washout as factors and baseline MSSBP or MSDBP as covariate.
* p-value < 0.05

Reviewer's comment:
The FDA statistical reviewer also conducted a sub-group analysis by region. The result showed patients who received valsartan/amlodipine exhibited greater reduction in change from baseline in MSSBP at week 4 than did those who received amlodipine in both U.S and non-US populations.

Sub-group Analysis by Region

Region	Treatment	N	Baseline Mean	LSM Change from Baseline	Difference	95% CI
US	Val/Aml	92	169.80	-32.16	-8.57	-12.35, -4.79
	Amlodipine	95	171.70	-23.59		
Non-Us	Val/Aml	226	170.33	-29.94	-5.99	-8.41, -3.56
	Amlodipine	226	170.45	-23.95		

Exploratory analysis results:
Overall blood pressure control was defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg. At Week 4 (LOCF), there were significantly greater proportions of patients who achieved overall blood pressure control in the valsartan/amlodipine group than in the amlodipine group (44.7% vs. 23.7%). This was also true at Weeks 2, 4 and 8.

Table 24 Proportion of unadjusted overall BP control by week and treatment strategy (ITT population)

Timepoint	Treatment	n	No. (%) of BP controlled [1]	95% CI*
Week 2	Val/Aml 160/10 mg (N=318)	317	91 (28.7)	(23.73, 33.69)
	Amlodipine 10 mg (N=321)	320	45 (14.1)	(10.25, 17.87)
Week 4	Val/Aml 160/10 mg (N=318)	307	139 (45.3)	(39.71, 50.85)
	Amlodipine 10 mg (N=321)	307	73 (23.8)	(19.02, 28.54)
Week 8	Val/Aml 160/10 mg (N=318)	296	157 (53.0)	(47.35, 58.73)
	Amlodipine 10 mg (N=321)	299	93 (31.1)	(25.86, 36.35)

N is the number of patients in ITT population; n is the number of ITT patients with a non-missing measurement at that timepoint.
[1] overall BP control defined as MSSBP < 140 mmHg and MSDBP < 90 mmHg.
* The asymptotic confidence intervals are presented.

One hundred patients had been expected to undergo ABPM. Although 92 patients had ABPM at baseline, only 76 (43 in the valsartan/amlodipine group, and 33 in the amlodipine group) had both baseline and post-baseline assessments.

Results for the between-treatment analysis of mean ambulatory systolic and diastolic blood pressure showed that valsartan/amlodipine was significantly more effective than amlodipine at Week 4 for both parameters. This is consistent with the results observed for the change from baseline in MSSBP and MSDBP described above.

Table 25 Between treatment analysis results for change from baseline in mean ambulatory blood pressure at Week 4 by treatment strategy (ABPM population)

Variable	Treatment	Baseline mean	LSM change (SEM)	Difference [1]	95% CI	p-value
MASBP (mmHg)	Val/Aml 160/10 mg (N=43)	138.8	-15.68 (0.81)	-5.73	(-8.0,-3.5)	<.0001
	Amlodipine 10 mg (N=33)	137.5	-9.94 (0.86)			
MADBP (mmHg)	Val/Aml 160/10 mg (N=43)	82.0	-8.99 (0.51)	-4.10	(-5.5,-2.7)	<.0001
	Amlodipine 10 mg (N=33)	82.5	-4.89 (0.54)			

[1] Difference is val/aml 160/10 mg minus amlodipine 10 mg
Least square means and the associated standard errors, confidence intervals and p-values were from a repeated-measures analysis of covariance with treatment, country, length of washout, post dosing hour and treatment by post-dosing hour as fixed factors and baseline mean 24- hour ambulatory SBP as a covariate and autoregressive order 1 covariance structure (AR1).
*indicates statistical significance at 0.05 level.

Patients randomized in this study received either valsartan/amlodipine 160/5 mg or amlodipine 5 mg for two weeks, and then were force-titrated to receive an additional 5 mg of amlodipine at Week 4. They remained on this dose for the remaining 6 weeks of the 8-week double-blind period. Although both treatment strategies produced clinically meaningful reductions in blood pressure, valsartan/amlodipine combination therapy was reduced and controlled blood pressure at all efficacy measures and all timepoints.

6.1.5 Clinical Microbiology
NA

6.1.6 Efficacy Conclusions

Two studies (CVAA489A 2402 and CVAA489A2403) were submitted in this sNDA for efficacy in Stage II hypertension. Both studies showed valsartan/amlodipine improved efficacy over amlodipine alone. However, these studies are limited for several reasons which include the fact that Exforge is compared only to amlodipine, the primary endpoint is the reduction of the systolic blood pressure not the diastolic, and ultimately hydrochlorothiazide was added to patients who did not reach goal. Also, the placebo effect was not subtracted.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Valsartan has been marketed as monotherapy for hypertension since 1996 in doses up to 320 mg. Amlodipine is administered as monotherapy in doses up to 10 mg. Since approval as combination therapy in June 2007, there have been no new unexpected adverse reactions.

7.1.1 Deaths

There were no deaths in either study A2402 or A2403.

7.1.2 Other Serious Adverse Events

Table 26 Number (percent) of patients with most frequent AEs in Study A2402

Adverse events (Preferred terms)	Val/Aml N=286 n (%)	Amlodipine N=285 n (%)
Total no. (%) with AE(s)	127 (44.4)	129 (45.3)
Edema peripheral	36 (12.6)	27 (9.5)
Headache	12 (4.2)	15 (5.3)
Dizziness	7 (2.4)	7 (2.5)
Nausea	7 (2.4)	2 (0.7)
Edema	7 (2.4)	6 (2.1)
Nasopharyngitis	6 (2.1)	7 (2.5)
Bronchitis	4 (1.4)	0 (0.0)
Diarrhea	4 (1.4)	7 (2.5)
Fatigue	4 (1.4)	1 (0.4)
Gastritis	4 (1.4)	2 (0.7)
Influenza	4 (1.4)	1 (0.4)
Muscle spasms	4 (1.4)	6 (2.1)
Pain in extremity	4 (1.4)	5 (1.8)
Upper respiratory tract infection	4 (1.4)	6 (2.1)
Back pain	3 (1.0)	3 (1.1)
Erectile dysfunction	3 (1.0)	1 (0.4)
Pruritus	3 (1.0)	3 (1.1)
Rhinitis allergic	3 (1.0)	1 (0.4)
Sinus congestion	3 (1.0)	0 (0.0)
Arthralgia	2 (0.7)	5 (1.8)
Joint swelling	2 (0.7)	3 (1.1)
Neck pain	2 (0.7)	3 (1.1)
Pharyngolaryngeal pain	2 (0.7)	3 (1.1)
Pollakiuria	2 (0.7)	4 (1.4)
Sinusitis	2 (0.7)	3 (1.1)
Constipation	1 (0.3)	8 (2.8)
Dry mouth	1 (0.3)	3 (1.1)
Abdominal pain	0 (0.0)	3 (1.1)
Hypokalemia	0 (0.0)	9 (3.2)
Toothache	0 (0.0)	4 (1.4)

Table 27 Number (percent) of patients with most frequent AEs in Study A2403

Preferred term	Val/Aml N = 321 n (%)	Amlodipine N = 323 n (%)
Total no. (%) with an AE	113 (35.2)	120 (37.2)
Edema peripheral	41 (12.8)	57 (17.6)
Headache	12 (3.7)	10 (3.1)
Nasopharyngitis	9 (2.8)	6 (1.9)
Asthenia	5 (1.6)	1 (0.3)
Abdominal pain upper	4 (1.2)	1 (0.3)
Dizziness	4 (1.2)	1 (0.3)
Gastroenteritis	4 (1.2)	0 (0.0)
Joint swelling	4 (1.2)	3 (0.9)
Cough	3 (0.9)	5 (1.5)
Diarrhea	3 (0.9)	6 (1.9)
Urinary tract infection	2 (0.6)	4 (1.2)
Dyspepsia	1 (0.3)	4 (1.2)
Flushing	1 (0.3)	4 (1.2)
Hypokalemia	1 (0.3)	4 (1.2)

Reviewer's comment:
It is interesting to note in the above 2 tables in both studies it is apparent that there is a higher percent of patients with peripheral edam on the combination than with amlodipine alone.

7.1.3 Dropouts and Other Significant Adverse Events

Table 2 8 Number (percent) of patients who had SAEs in Study A2402

Total number of patients studied	Val/Aml N=286 n (%)	Amlodipine N=285 n (%)
Deaths	0 (0.0)	0 (0.0)
Patients with serious AEs:		
Non-fatal SAEs	3 (1.0)	3 (1.1)
Drug related SAEs	1 (0.3)	0 (0.0)
Patients with other significant AEs:		
AEs suspected to be study drug related	50 (17.5)	38 (13.3)
AEs leading to study drug dose adjustment/interruption	3 (1.0)	2 (0.7)
Discontinuations due to:		
Any AEs including SAEs	7 (2.4)	9 (3.2)
SAEs	1 (0.3)	0 (0.0)
AEs (non-serious)	6 (2.1)	9 (3.2)
AEs suspected to be study drug related	6 (2.1)	6 (2.1)

Table 29 Number (%) of patients who had SAEs and other significant AEs in Study A2403

Total number of patients studied	Val/Aml N=321 n(%)	Amlodipine N=323 n(%)
Deaths	0 (0.0)	0 (0.0)
SAEs	3 (0.9)	0 (0.0)
Discontinuations due to:		
Any AEs including SAEs	19 (5.9)	19 (5.9)
SAEs	3 (0.9)	0 (0.0)
AEs suspected to be study drug related	13 (4.0)	19 (5.9)
Patients with other significant AEs:		
AEs leading to study drug dose adjustment/interruption	6 (1.9)	4 (1.2)

The most frequently reported reasons for discontinuation were lost to follow-up, withdrawal of consent, AEs, and protocol deviations. Lost to follow-up occurred more often in the valsartan/amlodipine treatment strategy than in the amlodipine treatment strategy; other reasons for discontinuation occurred at similar frequencies in both treatment strategies.

7.1.3.3 Other significant adverse events

Table 30 Adverse events potentially related to low blood pressure Study A2402

	Val/Aml N=286	Amlodipine N=285
Dizziness	7 (2.4%)	7 (2.5%)
Orthostatic hypotension	1 (0.3%)	0 (0.0%)
Vertigo	1 (0.3%)	0 (0.0%)

Table 31 Adverse events potentially related to low blood pressure Study A2403

	Val/Aml N=321	Amlodipine N=323
Dizziness	4 (1.2%)	1 (03.%)
Syncope	3 (0.9%)	0 (0.0%)
Hypotension	1 (0.3%)	0 (0.0%)

7.1.7 Laboratory Findings

7.1.7.1 Study A2402:

In Study A2402 the mean and median changes from baseline at endpoint (Week 12) were clinically unremarkable in all treatment strategies for the hematology parameters. Also, in the biochemistry parameters both mean and median changes from baseline at Weeks 4, 8, 12 and endpoint were clinically the same in both groups. The biochemistry parameters with the largest proportions of patients with clinically notable abnormalities were BUN, calcium, glucose and potassium. Clinically notable decreases in calcium and increases in potassium were observed at similar frequencies in both treatment strategies. Clinically notable increases in BUN and calcium occurred more often in the valsartan/amlodipine treatment strategy than in the amlodipine treatment strategy. Clinically notable increases in glucose and bilirubin and decreases in potassium occurred more often in the amlodipine treatment strategy than in the valsartan/amlodipine treatment strategy.

7.1.7.2 Study A2403:

In Study A2403 mean and median changes from baseline at endpoint were clinically unremarkable in all treatment strategies for the hematology parameters. For the biochemistry parameters mean and median changes from baseline at endpoint were clinically unremarkable in both groups. The biochemistry parameters with the largest proportions of patients with clinically notable abnormalities were potassium and calcium. Clinically notable increases in calcium and potassium were observed at similar frequencies in both treatment strategies. Clinically notable decreases in potassium occurred more often in the amlodipine treatment strategy (9.8%) than in the valsartan/amlodipine treatment strategy (3.6%). Otherwise, the frequencies of patients exhibiting clinically notable changes from baseline were generally similar for both treatment strategies.

7.1.8 Vital Signs

7.1.8.1 Study A2402:

The incidence of patients with orthostatic blood pressures is summarized in the table below. A criteria of a decrease of at least 20 mmHg in systolic blood pressure or a decrease of at least 10 mmHg in diastolic blood pressure when a patient moves from a sitting position to a standing position was used to define orthostatic blood pressure changes. A total of 25 patients (8.7%) in the valsartan/amlodipine treatment strategy and 24 patients (8.4%) in the amlodipine treatment strategy met the criteria at any post-baseline visit. At the earliest evaluated timepoint of 2 weeks, the incidence rates were also comparable between groups.

Table 32 Frequency of orthostatic blood pressure changes in Study VAA2402

Timepoint	Val/Aml N=286 n (%)	Amlodipine N=285 n (%)
Any [1]	25 (8.7)	24 (8.4)
Week 2	8 (2.8)	10 (3.5)
Week 4	12 (4.2)	3 (1.1)
Week 8	6 (2.1)	9 (3.2)
Week 12	7 (2.4)	9 (3.2)
Endpoint [2]	10 (3.5)	10 (3.5)

Orthostatic blood pressure is defined as a reduction in MSSBP of at least 20 mmHg or a reduction in MSDBP of at least 10 mmHg immediately after standing (or 3 min after standing) compared to the measurements taken in sitting position.
[1] Orthostatic blood pressure at any post-baseline visit
[2] Endpoint is the value at Week 12 or LOCF value

7.1.8.2 Study A2403:

The incidence of orthostatic blood pressure changes was similar in both treatment strategies. Fourty-three patients (13.4%) in the valsartan/amlodipine treatment strategy and 47 patients (14.6%) in the amlodipine treatment strategy met the criteria at any post-baseline visit. Even at the early timepoints, the incidence rates were also comparable between groups as seen in the table below.

Table 33 Orthostatic blood pressure changes in StudyA2403

	Val/Aml (N=321)		Amlodipine (N=323)	
Timepoint	Base	Post	Base	Post
Baseline	44 (13.7)		30 (9.3)	
Any [1]	6 (1.9)	43 (13.4)	4 (1.2)	47 (14.6)
Week 2	4 (1.2)	18 (5.6)	1 (0.3)	18 (5.6)
Week 4	1 (0.3)	15 (4.7)	1 (0.3)	14 (4.3)
Week 8	2 (0.6)	16 (5.0)	3 (0.9)	19 (5.9)
Endpoint [2]	4 (1.2)	23 (7.2)	4 (1.2)	27 (8.4)

Orthostatic blood pressure is defined as a reduction in MSSBP of at least 20 mmHg or a reduction in MSDBP of at least 10 mmHg immediately after standing (or 3 min after standing) compared to the measurements taken in sitting position.
[1] Orthostatic blood pressure at any post-baseline visit
[2] Endpoint is the value at Week 8 or LOCF value

7.2 Safety Conclusion
The observed safety profile of initial therapy with valsartan/amlodipine is consistent with the known pharmacological response of an angiotensin receptor blocker (valsartan) and a calcium channel blocker (amlodipine). The overall incidence rates of AEs, SAEs and AEs leading to discontinuation were similar with valsartan/amlodipine administered as initial therapy compared to amlodipine monotherapy. The incidence of AEs potentially related to low blood pressure was low with combination therapy and comparable to amlodipine monotherapy.

9 OVERALL ASSESSMENT

9.1 Conclusions

This sNDA was first submitted as a change in the original label from treating patients for hypertension who did not reach control with either valsartan or amlodipine alone to treatment as initial therapy for hypertension. Two additional studies for Stage II hypertension were also submitted which are reviewed here. These studies are limited for several reasons which include the fact that Exforge is compared only to amlodipine, the primary endpoint is the reduction of the systolic blood pressure not the diastolic, and ultimately hydrochlorothiazide was added to patients who did not reach goal. Also, the placebo effect was not subtracted. Therefore, these reviewers believe that the label should include Exforge as initial treatment for hypertension but that these additional studies are only approvable.

9.2 Recommendation on Regulatory Action

Approvable

9.3 Recommendation on Postmarketing Actions

NA

9.4 Labeling Review

To be reviewed separately.

9.5 Comments to Applicant

NA

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

/s/

Ququan Liu
6/30/2008 01:43:23 PM
BIOMETRICS

James Hung
7/8/2008 08:09:44 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

OTHER REVIEW(S)

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 21-990 BLA#	NDA Supplement #:S- 003 BLA STN #	Efficacy Supplement Type SE- 1
Proprietary Name: Exforge Established/Proper Name: amlodipine and valsartan Dosage Form: Tablet Strengths: 5/160, 10/160, 5/320, and 10/320 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: 9/24/07 Date of Receipt: 9/24/07 Date clock started after UN:		
PDUFA Goal Date: 7/24/08	Action Goal Date (if different):	
Filing Date: 11/24/07 Date of Filing Meeting: 11/8/07		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***		☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐		☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:		☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR

	601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 65,174	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☐ YES # years requested: ☒ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES ☐ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☒ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms*** *include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted): waiver granted	☐ YES ☒ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☐ YES ☒ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	☒ YES ☐ NO

Note: *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
REMS consulted to OSE/DRISK? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: Refer to Preliminary Responses for 5/30/07 Guidance Meeting, which was cancelled.	☐ YES Date(s): ☒ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**:	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/8/07

NDA/BLA #: 21-990/S-003

PROPRIETARY/ESTABLISHED NAMES: Exforge (amlodipine and valsartan) Tablets

APPLICANT: Novartis Pharmaceuticals Corporation

BACKGROUND: This efficacy supplement provides for the use of Exforge for the initial treatment of hypertension. Exforge was originally approved for the treatment of hypertension on June 20, 2007.

This sNDA submission consists of a Clinical Overview document and supporting analyses, as well as proposed revisions to the PI and PPI for Exforge. (Note: An Environmental Asessessment will be requested from the sponsor.)

No PK/PD or nonclinical pharmacology studies were conducted in support of this submission.

PLR and SPL labeling were submitted. Consult requests were sent to DDMAC, OSE, and SEALD for review of the proposed labeling. No changes were proposed to the carton/container labeling.

Only 3 reviews are needed: medical, statistical, and CMC (for Environmental Assessment).

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Quynh Nguyen	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Gail Moreschi	Y
	TL:	Abraham Karkowsky	N
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:		
	TL:		
Biostatistics	Reviewer:	Ququan (Cherry) Liu	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:	Nallamperumal Chidamabaram	N
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Norman Stockbridge, Ellis Unger, Anna Park-Hong

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: At the time of submission, this sNDA contained re-analyses of the data for studies previously submitted.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: EA will be requested in 74-day Letter.	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☒ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☒ NO ☐ YES ☐ NO

FACILITY (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division

GRMP Timeline Milestones: TBD

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

Quynh Nguyen
7/31/2008 11:04:15 AM
CSO

RHPM Overview – AP action
NDA 21-990/SE1-003
Exforge (amlodipine and valsartan) Tablets
5/160, 10/160, 5/320, and 10/320 mg

Sponsor:	Novartis Pharmaceuticals Corporation
Classification:	Standard
Submission Date:	September 24, 2007
Receipt Date:	September 24, 2007
User Fee Goal Date:	July 24, 2008

Background
This supplemental new drug application proposes the use of Exforge Tablets as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals. Exforge was initially approved for the treatment of hypertension on June 20, 2007.

The sNDA submission consists of a Clinical Overview document and supporting analyses of previously submitted studies, as well as two new studies.

No PK/PD or nonclinical pharmacology studies were conducted in support of this submission.

Proposed revisions to the PI and PPI in PLR and SPL format were submitted. Consult requests were sent to DDMAC, OSE, and SEALD for a review of the proposed labeling. No changes were proposed to the carton/container labeling.

During the 11/8/07 Filing Meeting, it was determined that only 3 reviews were needed: medical, statistical, and CMC [for the Environmental Assessment (EA)].

In our Filing Communication Letter to the sponsor, we requested additional data analyses per the "Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs" document. Additionally, updated labeling, an EA, and the sponsor's pediatric drug development plans were requested.

Chemistry Review
In his 7-17-08 review, Dr. Chidambaram wrote the following:

> COMMENTS
> This drug is currently approved for the treatment of hypertension. The current application is to seek approval to use Exforge in the initial treatment of hypertension. No new CMC information was submitted in this application. There are no changes proposed to the "Description" and "How Supplied" sections of labeling.
>
> The applicant submitted an environmental assessment document where the expected introduction concentration (EIC) for amlodipine and Valsartan are reported to be 0.25 ppb and 10.49 ppb respectively. Based on the above, a consult was sent to OPS to evaluate the EA document.
> Dr. Raanan Bloom is his review dated July 15th has determined no significant adverse environmental impacts are expected from the introduction of amlodipine and valsartan residues into the environment.
>
> CONCLUSIONS AND RECOMMENDATIONS
> Based on the above, this supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.

Medical and Statistical Reviews
A Joint Clinical and Statistical Review was completed. In their 6/30/08 review, Drs. Moreschi and Liu recommended an "Approvable" action and wrote the following:

> This sNDA was first submitted as a change in the original label from treating patients for hypertension who did not reach control with either valsartan or amlodipine alone to treatment as initial therapy for hypertension. Two additional studies for Stage II hypertension were also submitted which are reviewed here. These studies are limited for several reasons which include the fact that Exforge is compared only to amlodipine, the primary endpoint is the reduction of the systolic blood pressure not the diastolic, and ultimately hydrochlorothiazide was added to patients who did not reach goal. Also, the placebo effect was not subtracted. Therefore, these reviewers believe that the label should include Exforge as initial treatment for hypertension but that these additional studies are only approvable.

Division of Scientific Investigations (DSI)
As agreed to during the Filing meeting, a DSI inspection was not needed.

Pediatrics
The sponsor submitted a request for a full waiver of the pediatric requirement on 1-29-08. As previously discussed with the Agency, no pediatric studies of the combination of valsartan and HCTZ were planned.

A PeRC Committee meeting was held on 7-9-08. A full pediatric waiver is being granted for the following reason:

> The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
>
> **Justification:** Exforge is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by **The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**, *Pediatrics* 2004;114;555-576).

Financial Disclosure
In her 7/15/08 review, Dr. Moreschi wrote the following:

> Financial Disclosure regarding Studies A2402 and A2403
> None of the clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. No disclosable financial information was reported by any of the clinical investigators participating in the trials.

Safety Update
In her 7/15/08 safety update review, Dr. Moreschi wrote the following:

> Since approval of Exforge in June 2007, there have been no new unexpected adverse reactions.

Labeling
Draft labeling was submitted in PLR and SPL format. The proposed draft package insert is the first version to appear in PLR format for Exforge. No changes were proposed to the carton/container labeling.

DDMAC provided labeling recommendations in a review dated 6-26-08.

OSE-DRISK provided labeling recommendations in a review dated 7-10-08.

OSE-DMEPA provided labeling recommendations in a review dated 7-18-08.

SEALD did not provide labeling recommendations due to their limited resources, but referred us to the Tekturna HCT PI approved on 1-18-08 for the latest changes.

Pre-Approval Safety Conference
No Pre-Approval Safety Conference was held because there were no safety issues with this sNDA per the medical review and safety update review. This NDA is also a combination product with both components already approved.

Patent Information
The sponsor originally submitted this sNDA as a 505(b)(2) application and provided a Paragraph II certification. However, upon further consultation with Beth Duvall-Miller in the OND IO, it was determined that the sNDA is actually a 505(b)(1) application since Novartis conducted the original studies that they are now reanalyzing to support the sNDA.

User Fee
The user fee for this application was paid in full (User Fee ID #PD3007638).

CSO Summary
An approval (AP) on draft labeling letter will be drafted for Dr. Stockbridge's signature.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

QN/7-31-08

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

/s/

Quynh Nguyen
7/31/2008 11:01:38 AM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 18, 2008
To:	Norman Stockbridge, M.D. Division of Cardiovascular and Renal Products
Through:	Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention
From:	Cathy A. Miller, M.P.H., R.N. Safety Evaluator Division of Medication Error Prevention
Subject:	Labeling Review
Drug Name(s):	Exforge (Amlodipine Besylate and Valsartan) Tablets 5 mg/160, 10 mg/160 mg, 5 mg/320 mg, 10 mg/320 mg
Application Type/Number:	NDA 21-990
Submission Number:	SE1-003
Applicant:	Novartis Pharmaceutical Corporation
OSE RCM #:	2008-992

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EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the presentation of information in the revised package insert and patient package insert labeling for Exforge is vulnerable to confusion that could lead to medication errors. Specifically we note the omission of the unit of measure (mg) for the 5 milligram and 10 milligram component of the combination strength throughout labeling in the package insert and patient package insert labeling. We also identified the use of abbreviations that were not spelled out when initially introduced in the text, as well as the use of the dangerous abbreviation 'HCTZ' which is on the Institute for Safe Medication Practices' (ISMP) "List of Error-Prone Abbreviations, Symbols, and Dose Designations". To avoid ambiguity and misinterpretations, we recommend that the unit of measure always be included when expressing both components of the combination strengths of Exforge in package insert and patient package insert labeling. We also recommend that the abbreviation 'HCTZ' not be used in labeling and that other abbreviations be spelled out when initially introduced in the text of package insert labeling.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Cardiovascular and Renal Products to evaluate revised package insert and patient package insert labeling of Exforge for the potential to contribute to medication errors, specifically revisions to package insert and patient package insert labeling reflects the additional proposed indication of use were submitted for review.

1.2 REGULATORY HISTORY

Exforge (Amlodipine Besylate and Valsartan) oral tablets (NDA 21-990) was approved on June 20, 2007 for the indication of treatment of hypertension in patients not adequately controlled on monotherapy. On September 24, 2007, the applicant filed supplement (S-003) for an additional indication of use for treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve their optimal blood pressure. There are no changes in currently available strengths or recommended dosing frequency with this new indication of use.

1.3 PRODUCT INFORMATION

Exforge is a fixed combination of Amlodipine and valsartan. Exforge contains the besylate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype. Exforge is indicated for the treatment of hypertension in patients not adequately controlled on monotherapy. The expanded indication currently under review proposes an indication for the treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.

Exforge is available as a tablet formulated in four strengths for oral administration with a combination of amlodipine besylate and valsartan in combination strengths including 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg, and 10 mg/320 mg.

The usual starting dose of Exforge is 5 mg/160 mg once daily in patients who are not volume-depleted. The dosage can be increased after one to two weeks of therapy to a maximum of one 10 mg/320 mg tablet once daily as needed to control blood pressure. Exforge may also be used as add-on therapy for patients not controlled on monotherapy with either amlodipine (or another dihydropyridine calcium channel blocker), or with valsartan (or another angiotensin II receptor blocker) alone. Exforge may also be used as replacement therapy for those patients receiving amlodipine and valsartan from separate tablets and wish to receive tablets of Exforge containing the same component doses. For patients who experience

dose-limiting adverse reactions on monotherapy, they may be switched to Exforge containing a lower dose of that component.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

On June 25, 2008, the Division of Medication Error Prevention conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors involving Exforge have been reported. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredients (amlodipine and valsartan), trade name (Exforge), and verbatim terms 'Exf%'. Additionally, we performed an interaction search between Amlodipine and Valsartan, along with the trade name Exforge, to assure that any possible medication errors for this product could be identified and assessed.

The cases were manually reviewed to determine if medication errors occurred involving the label/labeling and/or nomenclature. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify contributing factors.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The package insert and patient package insert labeling is intended to communicate to practitioners and patients, all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because medication error prevention staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on March 31, 2008, the following labeling for our review:

---

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- Package Insert (PI)
- Patient Package Insert (PPI)

We reviewed the currently approved patient insert and patient packaging insert by Novartis Pharmaceuticals, Inc., dated April 2007, for the purpose of understanding the product characteristics and the details of Exforge and comparing them with the proposed revised package insert and patient package insert labeling.

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The Adverse Event Reporting System (AERS) search did not retrieve any medication error cases involving Exforge.

3.2 LABEL AND LABELING RISK ASSESSMENT

3.2.1 Package Insert Labeling

1. The dose ranges in the 'DOSAGE AND ADMINISTRATION' Section 2.1 General Considerations of the package insert are presented with a hyphen separating the low and high doses rather than spelling out the word 'to'.

2. There is no unit of measure (mg) presented for the 5 milligram and 10 milligram portion of the combination strengths throughout the text of Package Insert labeling.

3. The dangerous abbreviation 'HCTZ' is used throughout the clinical studies section of the package insert labeling.

4. Other abbreviations are used in the package insert labeling that have not been initially spelled out for the in the following locations:

   a. Section 5 WARNINGS AND PRECAUTIONS Subsection 5.1 Fetal/Neonatal Morbidity and Mortality : ACE

   b. Section 5.6 Congestive Heart Failure: NYHA

3.2.2 Patient Package Insert Labeling

1. There are no units of measure (mg) presented for the 5 milligram and 10 milligram portion of the combination strengths as presented in the patient package insert as follows:

   a. Section 17 PATIENT COUNSELING INFORMATION' Subsection 17.1 'Information for Patients'

4 DISCUSSION

The results of the Label and Labeling Risk Assessment performed by the Division of Medication Error Prevention found that information presented in the package insert and patient package insert appear to be vulnerable to confusion that could lead to medication errors. We note that a hyphen is currently used to separate the lower and higher end of dose ranges in the dosage and administration section of the package insert. To provide maximum clarity and avoid misinterpretation, the presentation of the dose ranges should be separated with the word 'to' rather than a hyphen.

Additionally, the omission of the units of measure for the 5 milligram and 10 milligram component of the combination strengths for Exforge provides a presentation of the combination strengths that reads: 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg. Because the unit of measure is not included on the 5 and

10 milligram portion of the combination strength, there is potential for dose/strength confusion if the (5) or (10) are overlooked or are misread as a quantity rather than a portion of the combination strength.

We note that the abbreviation 'HCTZ' appears in the clinical trials section of the labeling. 'HCTZ' appears on the Institute for Safe Medication Practices' (ISMP) "List of Error-Prone Abbreviations, Symbols, and Dose Designations". In June 2006, the Institute for Safe Medication Practices (ISMP) and the Food and Drug Administration launched a national education campaign to eliminate preventable sources of medication errors that occur from the use of ambiguous medical abbreviations. Post-marketing experience has shown that medication errors have occurred due to the misinterpretation of abbreviations used in prescribing practices, specifically with the abbreviation of hydrochlorothiazide (HCTZ).

Finally, we note that abbreviations were identified in the package insert labeling that were not spelled out when first introduced in the text of the document. Though it is unlikely that medication errors may occur from the abbreviations 'ACE' or 'NYHA', we recommend that abbreviations be spelled to avoid name confusion and provide a clear interpretation of the words.

5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed package insert and patient package insert labeling introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labeling, and the review of post-marketing medication error reports, the Division of Medication Error Prevention has identified areas of needed improvement. We have provided the following recommendations in Section 6.2 and request this information be forwarded to the Applicant.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, Project Manager, at 301-796-1332.

6.2 COMMENTS TO THE APPLICANT

Package Insert Labeling

1. Replace the hyphen with the word 'to' when describing a dose range for better clarity and to decrease ambiguity, as indicated below:

> Section 2.1 General Considerations
>
> Amlodipine is an effective treatment of hypertension in once daily doses of 2.5 mg to10 mg while valsartan is effective in doses of 80 mg to 320 mg. In clinical trials with Exforge® (amlodipine and valsartan) using amlodipine doses of 5 mg to 10 mg and valsartan doses of 160 mg to 320 mg, the antihypertensive effects increased with increasing doses.

2. Add the unit of measure to the 5 milligram and 10 milligram component of the combination strength wherever they appear in the text of the package insert and patient package insert labeling to read 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg , 10 mg/320 mg.

3. Do not use dangerous abbreviations that appear on the Institute for Safe Medication Practices (ISMP) "List of Error-Prone Abbreviations, Symbols, and Dose Designations" (i.e. HCTZ). In June 2006, the Institute for Safe Medication Practices and the Food and Drug Administration launched a national education campaign to eliminate preventable sources of medication errors that occur from the use of ambiguous medical abbreviations.

4. Spell out abbreviations (e.g. NYHA and ACE) when initially introduced in the text of the package insert.

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

/s/

Cathy A Miller
7/18/2008 03:44:07 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/18/2008 04:25:25 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 10, 2008
To:	Norman Stockbridge, M.D., PhD., Director **Division of Cardiovascular and Renal Products**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Exforge (amlodipine and valsartan) Tablets
Application Type/Number:	NDA 21-990
Submission Number:	S-003
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2008-992

1 INTRODUCTION

Novartis Pharmaceuticals Corporation submitted an efficacy supplement to their New Drug Application, sNDA 21-990/S-003, on March 31, 2008. The supplement proposes a new indication for Exforge (amlodipine and valsartan) Tablets, for the initial treatment of hypertension.

The Division of Cardiovascular and Renal Products requested that the Patient Labeling and Education Team review the revised Patient Package Insert (PPI) for Exforge (amlodipine and valsartan) Tablets. This review is written in response to that request. OSE previously reviewed the Exforge PPI on November 28, 2006.

2 MATERIAL REVIEWED

- EXFORGE Professional Information (PI) submitted by the sponsor on March 31, 2008 and further revised by the review division on July 8, 2007
- EXFORGE PPI submitted by the sponsor on March 31, 2008 and further revised by the review division on July 8, 2008.

3 DISCUSSION

The purpose of patient information leaflets is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI submitted by the sponsor has a Flesch Kinkaid grade level of 6.9, and a Flesch Reading Ease score of 67.9%. To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable.

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible,
- made the PPI consistent with the PI,
- rearranged information due to conversion of the PI to PLR format,
- removed unnecessary or redundant information
- Although not required for Patient Information, we have put this PPI in the question–and-answer format specified in the Medication Guide Regulations (21 CFR 208.20) that we recommend for all FDA approved patient labeling.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATIONS

1. As stated in our prior PPI review: A PPI for Exforge is voluntary. Except where products are dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. The available packaging for Exforge does not appear to be unit-of-use. The sponsor should clarify how they intend to distribute the PPI to patients.
2. We placed the pregnancy information in the section "What is the most important information I should know about EXFORGE?" into a black box to better reflect the Professional Information.
3. In the section "What is EXFORGE?"
    - We revised the indication statement to be more consistent with the PI. Consult with DDMAC to determine if the proposed indication statement is too broad in the PPI. This follows the recommendation in our review of the DIOVAN HCT PPI.
    - We moved the information about hypertension to the end of the PPI in a new section called "What is high blood pressure (hypertension)?". The information in the PPI should focus on the product, not the disease.
4. The section "Who should not take EXFORGE?" was deleted. There are no labeled contraindications to use. An allergy statement was added to the section "What should I tell my doctor before taking EXFORGE?"
5. At the end of the section "What should I tell my doctor before taking EXFORGE" the last paragraph instructs patients to stop taking beta blockers slowly. This information should be added to the PI in section 17 Patient Counseling Information.
6. Allergic reactions are not included in the Warnings and Precautions section (5) of the PI. Hypersensitivity is listed at the end of section 6.1 as isolated cases of certain clinically notable adverse reactions. The sponsor should clarify why only hypersensitivity was selected out of this list to be included in the PPI. If hypersensitivity is to remain in the PPI, the symptoms of hypersensitivity that have been seen in clinical trials should be added to the PI. The reportable signs and symptoms should be added to the PPI based on this. The language in the PPI must be consistent with the language in the PI.

7. We added the following statement to the end of the section, "What are the possible side effects of Exforge":

    Call your doctor for medical advice about side effects.
    You may report side effects to FDA at 1-800-FDA-1088.

    This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like Exforge, we recommend adding this language to all FDA-approved patient labeling for consistency.

Please let us know if you have any questions.

11 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Sharon Mills
7/10/2008 02:58:41 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
7/10/2008 08:02:55 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

To: Quynh Nguyen, PharmD, Regulatory Health Project Manager
Division of Cardiovascular and Renal Products, HFD-110

From: Lisa Hubbard, R.Ph., Regulatory Review Officer
DDMAC, HFD-42

Date: June 26, 2008

Re: Comments on draft labeling:
NDA 21-990
Exforge (amlodipine and valsartan) Tablets

DDMAC has reviewed the proposed package insert for NDA 21-990, Exforge (amlodipine and valsartan) Tablets for initial treatment of hypertension and offers the following comments with regard to promotional considerations:

Section 1 INDICATIONS AND USAGE

We note that the description of outcomes from the initial therapy studies for Exforge is presented in the proposed package insert (PI) as, "Predicted Percentage of Patients." The Avalide label describes similar outcomes in terms such as, "Probability of Achieving." We also note that the Avalide label provides a more descriptive explanation of how the initial therapy results should be interpreted, including an example for a given patient. Please confirm that these differences are essential based on the differences in the composition of the data supporting the new indication. Otherwise, please consider using language similar to the Avalide label in order to prevent misleading promotion of Exforge.

Section 12.3 Pharmacokinetics/*Pediatric:*

Section 12.3 of the proposed PI for Diovan HCT [redacted] (b) (4) .

Section 14 Clinical Studies

DDMAC recommends creating a separate subsection within the proposed label with regard to Initial Therapy as presented in the proposed PI for Diovan HCT.

DDMAC notes that Section 6.1 ADVERSE REACTIONS/Exforge does not present any additional information regarding adverse reactions observed in the initial therapy studies for Exforge. Please consider incorporating information into the proposed PI regarding

the observed risks associated with Exforge when used for initial treatment of hypertension.

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/s/

Lisa Hubbard
6/26/2008 01:29:51 PM
DDMAC REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021990Orig1s003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-990 SUPPL # 003 HFD # 110

Trade Name Exforge Tablets

Generic Name amlodipine and valsartan

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known 7/23/08

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-787	Norvasc (amlodipine besylate) Tablets
NDA# 20-665	Diovan (valsartan) Capsules
NDA# 21-283	Diovan (valsartan) Tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies A2201, A2307, A2305, A2306 - original NDA
New studies A2402 and A2403

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☒ NO ☐

Investigation #2 YES ☒ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Studies A2201, A2307, A2305, A2306 - original NDA

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

New studies A2402 and A2403

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 65,174	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 65,174	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Quynh Nguyen, Pharm.D.
Title: Regulatory Health Project Manager, Division of Cardiovascular and Renal Products
Date: 7/31/08

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Norman Stockbridge

7/31/2008 03:18:19 PM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21-990	BLA STN# NDA Supplement # 003	If NDA, Efficacy Supplement Type SE1	
Proprietary Name: Exforge Established Name: amlodipine and valsartan Dosage Form: Tablets		Applicant: Novartis Pharmaceuticals Corporation	
RPM: Quynh Nguyen, Pharm.D.		Division: DCRP	Phone # 301-796-0510

NDAs: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 19-787 Norvasc (amlodipine beylate) Tablets Provide a brief explanation of how this product is different from the listed drug. Exforge is a combination product of amlodipine and valsartan tablets. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☒ Corrected Date: 7-22-08

❖ User Fee Goal Date ❖ Action Goal Date (if different)	7-24-08
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action

❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☒ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Division Director's Memo, 7-16-08
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	Included
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	Included
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 7-18-08 ☒ DSRCS 7-10-08 ☒ DDMAC 6-26-08 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	7-31-08; 7-31-08
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	7-17-08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☒ Review & FONSI *(indicate date of review)*	7-16-08; 7-18-08
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☐ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	6-30-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	7-15-08
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	7-15-08
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 6-30-08
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☒ None

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s Office of Regulatory Policy representative.

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

/s/

Quynh Nguyen
7/31/2008 11:05:53 AM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-990 Supplement Number: 003 NDA Supplement Type (e.g. SE5): SE1

Division Name:Cardiovascular and Renal Products PDUFA Goal Date: 7/24/08 Stamp Date: 9/24/07

Proprietary Name: Exforge

Established/Generic Name: amlodipine and valsartan

Dosage Form: Tablet

Applicant/Sponsor: Novartis Pharmaceuticals Corporation

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Treatment of hypertension. This fixed dose combination is not indicated for the initial therapy of hypertension.
(2) _____
(3) _____
(4) _____

Q1: Is this application in response to a PREA PMC? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMC #:_____

Does the division agree that this is a complete response to the PMC?

☐ Yes. **Skip to signature block.**

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Initial treatment of hypertension.

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☒ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may <u>only</u> cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover <u>all</u> of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 4/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for the remaining pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be ineffective or unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be ineffective or unsafe in this/these pediatric population(s) (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may <u>only</u> cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and F and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Sections D and F and complete the PeRC Pediatric Assessment form); and/or (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Sections E and F). Note that more than one of these options may apply for this indication to cover <u>all</u> of the pediatric subpopulations.

Section C: Deferred Studies (for remaining pediatric subpopulations). Complete Section F on Extrapolation.

Check pediatric subpopulation for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**	
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Yes	No
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through the partial waivers and deferrals, proceed to Section F. For those pediatric subpopulations for which studies have been completed, proceed to Sections D and F and complete the PeRC Pediatric Assessment form. For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F.

Section D: Completed Studies (for some or all pediatric subpopulations). Complete Section F on Extrapolation.

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: For those pediatric subpopulations for which additional studies are not needed because the drug is appropriately labeled in one or more pediatric subpopulations, proceed to Sections E and F. If there are no further pediatric subpopulations to cover based on the partial waivers, deferrals and completed studies, go to Section F.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations): (Complete section F)

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If studies are not needed because efficacy is being extrapolated from other adult and/or pediatric studies, proceed to Section F. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the target pediatric subpopulation needing studies. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 4/2008)

Pediatric Research and Equity Act Waivers

IND/NDA/BLA #: 21-990 Supplement Type: SE1 Supplement Number: 003

Product name and active ingredient/dosage form: Exforge (amlodipine and valsartan) Tablets

Sponsor: Novartis Pharmaceuticals Corporation

Indications(s): Initial treatment of hypertension.
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth to 16 years old

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

   c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

      Justification: Exforge is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by **The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**, *Pediatrics* 2004;114;555-576).

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/s/

Quynh Nguyen
7/18/2008 10:54:20 AM

Financial Disclosure regarding Studies A2402 and A2403

None of the clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. No disclosable financial information was reported by any of the clinical investigators participating in the trials.

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/s/

Gail Moreschi
7/15/2008 10:04:31 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OPS Staff (HFD-003)
Attn: Raanan Bloom (301-796-2185)
WO21 Rm 3515

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Swati Patwardhan, ONDQA, 301-796-4085

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 8, 2008		21-990	SE1-003	September 24, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Exforge			July 15, 2008

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

This efficacy supplement is located in the EDR at: \FDSWA150\NONECTD\N21990\S_003\2008-01-29

Please evaluate the EA submitted on 1/29/08. This supplement is due on July 24, 2008.

SIGNATURE OF REQUESTOR
Swati Patwardhan

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Swati A Patwardhan

7/8/2008 04:06:55 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE,
Attention: Sean Bradley, R.Ph.

FROM:
Quynh Nguyen, Project Manager
OND/Division of Cardiovascular and Renal Products (DCRP)
Ph: (301) 796-0510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6-13-07		21-990/SE1-003	sNDA submission	March 31, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Exforge (amlodipine and valsartan) Tablets	High	Anti-hypertensive	July 1, 2008

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- XX OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This efficacy supplement proposes a new indication for the initial treatment of hypertension. Could you please review the proposed labeling (PI and PPI) located in the EDR at: \\FDSWA150\NONECTD\N21990\S_003\2008-03-31 - see the labeling folder. [Note: Please see the PI for Avalide approved on 11-16-07 (NDA 20-758/S-037) and the PI for Diovan approved on 11-29-07 (NDA 21-283/S-024) as a reference]. I apologize for the short turnaround time. If you could let me know who they are, I will also invite the assigned OSE reviewer(s) to the internal labeling meetings in early July. Please let me know if you have any questions. Thanks!

PDUFA Goal Date: **July 24, 2008**

SIGNATURE OF REQUESTER Quynh Nguyen, RPM	METHOD OF DELIVERY (Check one) ☐ MAIL XX E-MAIL
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Quynh Nguyen

6/13/2008 01:13:27 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Lisa Hubbard, R.Rh., Regulatory Review Officer
OMP/Division of Drug Marketing, Advertisting, and Communications (DDMAC)

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Quynh Nguyen, Regulatory Health Project Manager
OND/Division of Cardiovascular and Renal Products
Ph: (301) 796-0510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6-13-08		21-990/S-003	NDA submission	March 31, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Exforge (amlodipine besylate/valsartan) Tablets	High	anti-hypertensive	July 1, 2008 or sooner

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This efficacy supplement proposes a new indication for the initial treatment of hypertension. Could you please review the proposed PI and Patient Package Insert located in the EDR at: \\FDSWA150\NONECTD\N21990\S_003\2008-03-31 - see the labeling folder. [Note: Please see the PI for Avalide approved on 11-16-07 (NDA 20-758/S-037) and the PI for Diovan that was approved on 11-29-07 (NDA 21-283/
S-024) as a reference]. I apologize for the short turnaround time. I will also invite you to the internal labeling meetings to be scheduled in early July. Please let me know if you have any questions. Thanks!

PDUFA Goal Date: 7/24/08

SIGNATURE OF REQUESTOR Quynh Nguyen, RHPM	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Quynh Nguyen
6/13/2008 12:19:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-990/S-003

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Ms. Donna M. Vivelo
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

Please refer to your September 24, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exforge (amlodipine and valsartan) 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg Tablets.

We also refer to your submission dated March 31, 2008.

We are reviewing the Statistical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental NDA.

1. It appears that your regression curves of the probability of reaching a blood pressure target were based on model fitting applied to all treatment groups jointly (i.e., with or without treatment by baseline interaction). We request that logistic modeling be performed separately on each treatment group (i.e., for each treatment group, the model contains intercept and baseline blood pressure only) and then put the curve for each treatment group on a single plot.

2. Please provide a histogram of the baseline distribution of blood pressure (systolic and diastolic) for each treatment group (monotherapy or combination).

3. For Study CVAA489A2402 and Study CVAA489A2403, please provide the analysis programs for the primary and secondary endpoints analyses.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge

5/6/2008 05:18:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-990/S-003

Novartis Pharmaceuticals Corporation
Attention: Ms. Donna Vivelo
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Vivelo:

Please refer to your new drug application (NDA) dated February 22, 2006, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Exforge (amlodipine and valsartan) 5/160, 10/160, 5/320, and 10/320 mg Tablets.

We also refer to your submission dated October 5, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 24, 2007 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. In addition to the regression curves for the probability of reaching blood pressure targets (140 and 130 mmHg systolic and 90 and 80 mm Hg diastolic) you submitted, please also submit model diagnostics plots and model fit information. For detail requirements, see the attached document entitled "**Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs**."

2. We note that your proposed labeling did not include the "Highlights of prescribing information" and "Full prescribing information: Contents" sections per 21 CFR 201.57(a) and (b). Please submit the proposed labeling that includes these sections.

3. Please submit an Environmental Assessment Document or a request for categorical exclusion from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement in accordance with 21 CFR Part 25.31(a).

4. All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have not addressed how you plan to fulfill this pediatric requirement. Please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Your pediatric drug development plans must address the following indication: use of Exforge for the initial treatment of hypertension.

If you believe that this drug qualifies for a full or partial waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation within 60 days from

the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Points to Consider in Generating Graphs for Initial Therapy with Combination Antihypertensive Drugs

This document is intended to provide general guidance for use of graphs in drug labeling for initial therapy with combination antihypertensive drugs. The four graphs are to illustrate the advantage of a combination drug over its component drugs in reaching blood pressure goals of 140 and 130 mm Hg systolic and 90 and 80 mm Hg diastolic.

The graph contains regression curves for the probability of reaching a blood pressure target after treatment as a function of baseline blood pressure for the treatment groups. The curves are often based on logistic regression modeling. Some other statistical models such as probit regression may be considered. For model fitting, the following statistical considerations need attention:

1. The regression curves should fit the data reasonably well with no disproportionate leverage exerted from extreme values or potential outliers. Extensive model diagnostics are required for assessment of goodness-of-fit or a lack of fit of the fitted model. To determine overall and local fit of each regression curve, the diagnostics should include comparison of the regression curve with a LOESS non-parametric curve, comparison of the regression curve with histogram, tests (e.g., Hosmer-Lemeshow test) for fit, analysis of potential influential values. Diagnostics plots need to be generated and should include those of residuals (e.g., chi-square residual, deviance residual) versus estimated probability of achieving the blood pressure goal, difference in beta parameter value versus estimated probability, etc. If a few extreme values are suspected to cause a lack of fit, the fit may be improved by trimming these data points for further assessment. However, how many and which data points should be removed is a subjective judgment. The process of removing a few subjects for further assessment of model fit is a part of influence diagnostics. The final graphs in the drug label should include all data if possible.

2. In general, the model parameters of each treatment group should be estimated only from the data of this treatment group. In some rare situation, a simpler model such as use of a common slope for all treatment groups might improve the precision of the curves. However, applying such a simpler model to all treatment groups in regression analysis relies on strong assumptions and thus it may induce model and selection biases. Comparisons among models via statistical model selection criteria (such as AIC) need to be made, in addition to the necessary model diagnostics described above.

3. Pooling studies is discouraged because it relies on many strong and unverifiable assumptions, such as the studies pooled employ an identical design and target the same patient population, etc. When the assumptions do not hold, the curves generated from the pooled studies can be very misleading.

4. One or two studies should be chosen for display in the case that there are multiple studies conducted and pooling studies is not viable. As a general principle, the pivotal trial with the largest sample size per treatment group should be first considered. If there are multiple dose combinations, the highest dose combination is first considered with its monotherapy doses.

5. Please provide an assessment of the representation of very elderly and other fragile patients among the subjects in the factorial studies, and their adverse event profile with and tolerability to randomization to the combination.

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/s/

Norman Stockbridge

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