DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022401/S-007 and S-009

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ms. Heidi C. Reidies
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Ms. Reidies:

Please refer to your Supplemental New Drug Applications (sNDA) dated June 9, 2011, received June 9, 2011 (S-007), and dated August 29, 2011, received August 29, 2011 (S-009) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Twynsta (telmisartan/amlodipine) 40/5, 40/10, 80/5, and 80/10 mg Tablets.

We acknowledge receipt of your amendments dated December 7, 2011 and April 12, 2012 for both sNDAs.

S-007
This "Prior Approval" supplemental new drug application provides for revisions to the **HIGHLIGHTS**, **Warnings and Precautions**, **Overdosage**, **Drug Interactions**, and **Pharmacodynamics** sections of the labeling. The revisions are based on the updated labeling for Norvasc® (amlodipine besylate) Tablets.

These changes have been made as follows (additions are shown as underlined text and deletions are shown as ~~strike-through text~~):

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

1. Under **RECENT MAJOR CHANGES**, the following changes were made:

----------RECENT MAJOR CHANGES----------	
Contraindications (4)	3/2012
Warnings and Precautions	
Hypotension (5.2)	10/2012
Risk of Myocardial Infarction or Increased Angina (5.7)	10/2012

2. Under **WARNINGS AND PRECAUTIONS**, the following changes were made to the 2nd, 5th, and 6th bullets:

- Hypotension: Correct any volume or salt depletion before initiating therapy. Observe for signs and symptoms of hypotension. Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis (5.2)
- Avoid concomitant use ~~of~~with an ACE inhibitor ~~and angiotensin receptor blocker~~ (5.6)

- Myocardial infarction: Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of TWYNSTA, particularly in patients with severe obstructive coronary artery disease ~~Uncommonly, initiating a CCB in patients with severe obstructive coronary artery disease may precipitate myocardial infarction or increased angina~~ (5.7)

In **FULL PRESCRIBING INFORMATION**

3. Under **5.2 Hypotension**, the following changes were made:

Amlodipine
Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely. ~~Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, observe patients with severe aortic stenosis closely when administering amlodipine, as one should with any vasodilator.~~

4. Under **5.7 Risk of Myocardial Infarction or Increased Angina**, the following changes were made:

Amlodipine
Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of TWYNSTA, particularly in patients with severe obstructive coronary artery disease. ~~Uncommonly, 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. Under **7.2 Drug Interactions with Telmisartan**, the following changes were made:

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. ~~It is, t~~Therefore, ~~recommended that~~monitor digoxin levels ~~be monitored~~ when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range~~to avoid possible over- or under-digitalization~~.

6. Under **7.3 Drug Interactions with Amlodipine**, the following changes were made starting with the 3rd paragraph:

The following have no clinically relevant effects on the pharmacokinetics of amlodipine: cimetidine, grapefruit juice, magnesium and aluminum hydroxide antacid~~Maalox®,~~ sildenafil.

Amlodipine has no clinically relevant effects on the pharmacokinetics or pharmacodynamics of the following: atorvastatin, digoxin, warfarin.

CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors.

CYP3A4 Inducers
No information is available on the quantitative effects of CYP3A4 inducers (*e.g., carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone, rifampicin, St. John's Wort)* on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers.

7. Under **10 OVERDOSAGE**, the following changes were made:

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 and possibly a reflex tachycardia. 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.~~

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

If massive overdose should occur, initiate active cardiac and respiratory monitoring ~~should be instituted~~. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids ~~should be initiated~~. If hypotension remains unresponsive to these conservative measures, consider 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.

8. Under **12.2 Pharmacodynamics**, the following sentence was added to the end of the *Telmisartan* subsection:

Telmisartan has indications other than hypertension which can be found in the Micardis® (telmisartan) tablets package insert.

9. Under **17.1 Pregnancy**, the following changes were made:

~~**FDA-Approved Patient Labeling**~~
~~Patient labeling is provided as a tear-off leaflet at the end of this prescribing information.~~

Norvasc is a registered trademark of Pfizer Inc.
~~Maalox is a registered trademark of Novartis.~~

S-009

This "Prior Approval" supplemental new drug application provides for revisions to the **HIGHLIGHTS** and **FULL PRESCRIBING INFORMATION** in the **INDICATIONS AND USAGE** and **CLINICAL STUDIES** sections of the labeling in accordance with the Guidance for Industry, *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims*, March 2011.

These changes have been made as follows (additions are shown as underlined text and deletions are shown as ~~strike-through text~~):

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

10. Under **RECENT MAJOR CHANGES**, the following changes were made:

----------RECENT MAJOR CHANGES----------	
Indications and Usage (1)	10/2012
Contraindications (4)	3/2012

11. Under **INDICATIONS AND USAGE**, the following changes were made:

- TWYNSTA is an angiotensin II receptor blocker (ARB) and a dihydropyridine calcium channel blocker (DHP-CCB) combination product indicated for the treatment of hypertension alone or with other antihypertensive agents to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions (1)

In **FULL PRESCRIBING INFORMATION**

12. Under **INDICATIONS AND USAGE**, the following changes were made:

TWYNSTA (telmisartan/amlodipine) tablets are indicated for the treatment of hypertension, alone or with other antihypertensive agents to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including angiotensin II receptor blockers and dihydropyridine calcium channel blockers. There are no controlled trials demonstrating risk reduction with TWYNSTA.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most

consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

13. Under **14 CLINICAL STUDIES**, at the end of the **14.1 TWYNSTA Tablets** subsection, the following sentence was added:

There are no trials of TWYNSTA demonstrating reductions in cardiovascular risk in patients with hypertension, but at least one pharmacologically similar drug has demonstrated such benefits.

Both S-007 and S-009
In **Patient Information**

14. Under the "**What is high blood pressure (hypertension)?**" section, the following changes were made:

> Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. TWYNSTA tablets can help your blood vessels relax so your blood pressure is lower. Medicines that lower your 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 the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure, and vision problems.

Minor editorial changes

15. In **HIGHLIGHTS OF PRESCRIBING INFORMATION**, under **RECENT MAJOR CHANGES**, the following changes were made:

----------RECENT MAJOR CHANGES----------	
Boxed Warning	3/2012
Indications and Usage (1)	10/2012
Contraindications (4)	3/2012
Warnings and Precautions	
Fetal Toxicity (5.1)	3/2012
Hypotension (5.2)	10/2012
Risk of Myocardial Infarction or Increased Angina (5.7)	10/2012

Note: The "Boxed Warning" and "Warnings and Precautions, Fetal Toxicity (5.1)" listings were inadvertently omitted from the **RECENT MAJOR CHANGES** in the last approved labeling supplement (S-011, approved March 29, 2012) and are being included in this supplement approval.

16. In **FULL PRESCRIBING INFORMATION**, vertical margin marks were added to the text for the **Boxed Warning** and **Warnings and Precautions, Fetal Toxicity (5.1)** to correspond to these **RECENT MAJOR CHANGES** listings in **HIGHLIGHTS**.

    Note: These vertical margin marks were inadvertently omitted in the last approved labeling supplement (S-011, approved March 29, 2012) and are being included in this supplement approval.

17. Minor editorial corrections were made.

18. The label number and revision dates have been updated.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 contact:

Quynh Nguyen, Pharm.D., RAC
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:
Content of Labeling

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

/s/

NORMAN L STOCKBRIDGE
10/19/2012