DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020364/S-047 **SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation
Attention: Nancy Price
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1448

Dear Ms. Price:

Please refer to your supplemental new drug application dated June 19, 209, received June 19, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lotrel (amlodipine besylate/benazapril hydrochloride) 2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg, and 10/40 mg Capsules.

We acknowledge receipt of your submission dated January 20, and February 18, 2010.

Your submission of February 18, 2010 constituted a complete response to our December 18, 2009 action letter.

This Prior Approval supplemental new drug application provides for conversion to the Physician Labeling Rule format (PLR), changes to the **FULL PRESCRIBING INFORMATION, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, USE IN SPECIFIC POPULATIONS, OVERDOSAGE, NONCLINICAL TOXICOLOGY, PATIENT COUNSELING INFORMATION** sections, and a change to the Patient Package Insert (PPI).

The following changes were made:

1. In **FULL PRESCRIBING INFORMATION**, the boxed warning was revised from:

(b) (4)

To:

WARNING: AVOID USE IN PREGNANCY

When pregnancy is detected, discontinue Lotrel as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (5.4)

2. In **INDICATIONS AND USAGE**, the following text was deleted:

(b) (4)

3. In **DOSAGE AND ADMINISTRATION**, the following text was deleted from the third and part of the fourth paragraphs:

The hazards [*see Warnings and Precautions* (b) (4)] of benazepril 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. When benazepril is added to a regimen of amlodipine, the incidence of edema is substantially reduced. Therapy with any combination of amlodipine and benazepril will thus be associated with both sets of dose-independent hazards, but the incidence of edema will generally be less than that seen with similar (or higher) doses of amlodipine monotherapy.

Rarely, the dose-independent hazards of benazepril are serious. To minimize dose-independent hazards...

4. (b) (4)

5. In **DOSAGE AND ADMINISTRATION**, the following text was deleted:

(b) (4) ***Replacement Therapy***

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

6. In **DOSAGE FORMS AND STRENGTHS**, the section was changed from:

(b) (4)

To:

Lotrel (amlodipine/benazepril) capsules are available as follows:

2.5/10 mg, 5/10 mg, 5/20 mg, 5/40 mg, 10/20 mg, and 10/40 mg.

7. In **CONTRAINDICATIONS**, the first paragraph was changed from:

(b) (4)

To:

Lotrel is contraindicated in patients with a history of angioedema, with or without previous ACE inhibitor treatment, or patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine.

8. In **WARNINGS AND PRECAUTIONS/Anaphylactoid and Possibly Related Reactions**, the following sentence has been added as the last sentence of the first paragraph:

Black patients receiving ACE inhibitors have a higher incidence of angioedema compared to nonblacks.

9. In **WARNINGS AND PRECAUTIONS/Anaphylactoid and Possibly Related Reactions**/***Head and Neck Angioedema,*** in the third sentence of the first paragraph, the passive voice has been converted to active voice. The sentence now reads:

Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, discontinue treatment with Lotrel and institute appropriate therapy immediately.

10. In **WARNINGS AND PRECAUTIONS/Increased Angina and/or Myocardial Infarction**, the word “and” was deleted from the first sentence of the first paragraph. The sentence now reads:

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.

11. In **WARNINGS AND PRECAUTIONS/Hypotension**, the following text was deleted:

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

12. In **WARNINGS AND PRECAUTIONS/Hypotension**, the passive voice was converted to active voice throughout the entire section. The section now reads:

> Lotrel can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting.
>
> In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, start Lotrel therapy under close medical supervision; follow closely for the first 2 weeks of treatment and whenever the dose of the benazepril component is increased or a diuretic is added or its dose increased.
>
> Symptomatic hypotension is also possible in patients with severe aortic stenosis.
>
> If hypotension occurs, place the patient in a supine position, and if necessary, treat with intravenous infusion of physiologic saline. Lotrel treatment usually can be continued following restoration of blood pressure and volume.

13. In **WARNINGS AND PRECAUTIONS/Neutropenia/Agranulocytosis**, in the third sentence of the first paragraph, the passive voice was converted to active voice. The sentence now reads:

> Consider monitoring of white blood cell counts in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

14. In **WARNINGS AND PRECAUTIONS/Fetal/Neonatal Morbidity and Mortality**, the section was changed from:

> ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Lotrel should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis.
>
> The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death.
>
> To:
>
> Lotrel 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, apprise the patient 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)]*

15. In **WARNINGS AND PRECAUTIONS/Hepatic Failure**, the first sentence in the third paragraph was changed from:

(b) (4)

To:

However, since amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, titrate Lotrel slowly in patients with severe hepatic impairment.

16. In **WARNINGS AND PRECAUTIONS/Impaired Renal Function,** the section was changed from:

Impaired Renal Function: Lotrel should be used with caution in patients with severe renal disease.
When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with **severe congestive heart failure**, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.
In a small study of hypertensive patients with **unilateral or bilateral renal artery stenosis**, treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with Lotrel, renal function should be monitored during the first few weeks of therapy.
Some benazepril-treated hypertensive patients with **no apparent preexisting renal vascular disease** have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of Lotrel may be required. **Evaluation of the hypertensive patient should always include assessment of renal function** (see DOSAGE AND ADMINISTRATION).

To:

Lotrel should not be used in patients with severe renal disease (Clearance creatinine < 30 ml/min), (Dosage and Administration, 2.1)

In patients with severe heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with benazepril may be associated with oliguria or progressive azotemia and (rarely) with acute renal failure and/or death.

In a small study of hypertensive patients with unilateral or bilateral renal artery stenosis, treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with Lotrel, monitor renal function during the first few weeks of therapy.

Some benazepril-treated hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of Lotrel may be required.

Renal function should be monitored periodically in patients receiving benazepril.

17. In **WARNINGS AND PRECAUTIONS**, the section [redacted] (b) (4) was deleted [redacted] (b) (4).

18. In **WARNINGS AND PRECAUTIONS/Cough**, in the second sentence of the first paragraph, the passive voice was converted to active voice. The sentence now reads:

    Consider ACE inhibitor-induced cough in the differential diagnosis of cough.

19. In **ADVERSE REACTIONS**, the title [redacted] (b) (4) was changed from:

    [redacted] (b) (4)

    To:

    Clinical Trials Experience

20. In **ADVERSE REACTIONS/Clinical Trials Experience**, the following text was added as the first paragraph:

    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.

21. In **ADVERSE REACTIONS/Clinical Trials Experience**, the following text was added as the fifth and sixth paragraphs respectively:

    The peripheral edema associated with amlodipine use is dose-dependent. When benazepril is added to a regimen of amlodipine, the incidence of edema is substantially reduced.

The addition of benazepril to a regimen of amlodipine should not be expected to provide additional antihypertensive effect in African-Americans. However, all patient groups benefit from the reduction in amlodipine-induced edema.

22. In **ADVERSE REACTIONS/** [redacted] (b) (4), the [redacted] (b) (4) paragraph was changed from:

    The incidence of edema was statistically greater in patients treated with amlodipine monotherapy than in patients treated with the combination. Edema and certain other side effects are associated with amlodipine monotherapy in a dose-dependent manner, and appear to affect women more than men. The addition of benazepril resulted in lower incidences as shown in the following table; the protective effect of benazepril was independent of race and (within the range of doses tested) of dose.

    To:

    The incidence of edema was greater in patients treated with amlodipine monotherapy (5.1%) than in patients treated with Lotrel (2.1%) or placebo (2.2%).

23. In **ADVERSE REACTIONS** [redacted] (b) (4), the following text was added to the list:

    Hematologic: Neutropenia

24. In **ADVERSE REACTIONS/** [redacted] (b) (4), the [redacted] (b) (4) paragraph was changed from:

    Monotherapies of benazepril and amlodipine have been evaluated for safety in clinical trials in over 6,000 and 11,000 patients, respectively. The observed adverse reactions to the monotherapies in these trials were similar to those seen in trials of Lotrel. In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) severe enough to require hospitalization have been reported in association with use of amlodipine. Other potentially important adverse experiences attributed to other ACE inhibitors and calcium channel blockers include: eosinophilic pneumonitis (ACE inhibitors) and gynecomastia (CCB's). **Clinical Laboratory Test Findings**

    To:

    Monotherapies of benazepril and amlodipine have been evaluated for safety in clinical trials in over 6,000 and 11,000 patients, respectively. The observed adverse reactions to the monotherapies in these trials were similar to those seen in trials of Lotrel.

25. In **ADVERSE REACTIONS**, the following text was added:

    6.2 Post-marketing Experience
    Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

26. In **DRUG INTERACTIONS/Drug-Drug Interactions/*Potassium Supplements and Potassium-Sparing Diuretics***, the first paragraph was changed from:

> Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.
>
> To:
>
> Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, the patient's serum potassium should be monitored frequently.

27. In **DRUG INTERACTIONS/Drug-Drug Interactions/*Lithium***, in the second sentence of the first paragraph the passive voice was converted to active voice. The sentence now reads:

> When co administering Lotrel and lithium frequent monitoring of serum lithium levels is recommended.

28. In **USE IN SPECIFIC POPULATIONS/Pregnancy**, the passive voice was converted to active voice throughout the entire section. The section now reads:

> The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.
>
> In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects. In women planning to become pregnant, ACE inhibitors (including benazepril) should not be used. Make women of childbearing age aware of the potential risk and give Lotrel only after careful counseling and consideration of individual risks and benefits.
>
> Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, apprise the mothers of the potential hazards to their fetuses, and perform serial ultrasound examinations to assess the intra-amniotic environment.
>
> If oligohydramnios is observed, discontinue Lotrel unless it is considered life saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of in utero exposure to ACE inhibitors for hypotension, oliguria, and hyperkalemia. If oliguria occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers, but experience is limited.

29. In **USE IN SPECIFIC POPULATIONS/Nursing Mothers**, the second sentence of the second paragraph was changed from:

    In the absence of this information, it is recommended that nursing be discontinued while Lotrel is being administered.

    To:

    Nursing or drug should be discontinued.

30. In **OVERDOSAGE**, the following text was deleted from the third paragraph:

    When mice were given single oral doses of benazepril/amlodipine, mortality was 20% at 50:25 mg/kg, 10% at 100:50 mg/kg, and 100% at 500:250 mg/kg. In rats, mortality was 25% (pooling two studies) at 500:250 mg/kg and 100% at 900:450 mg/kg.

31. In **OVERDOSAGE/*Treatment***, the second paragraph was changed from:

    The most likely effect of overdose with Lotrel is vasodilation, with consequent hypotension and tachycardia. Simple repletion of central fluid volume (Trendelenburg positioning, infusion of crystalloids) may be sufficient therapy, but pressor agents (norepinephrine or high-dose dopamine) may be required. Overdoses of other dihydropyridine calcium channel blockers are reported to have been treated with calcium chloride and glucagon, but evidence of a dose-response relation has not been seen, and these interventions must be regarded as unproven. With abrupt return of peripheral vascular tone, overdoses of other dihydropyridine calcium channel blockers have sometimes progressed to pulmonary edema, and patients must be monitored for this complication.

    To:

    The most likely effect of overdose with Lotrel is vasodilation, with consequent hypotension and tachycardia. Simple repletion of central fluid volume (Trendelenburg positioning, infusion of crystalloids) may be sufficient therapy, but pressor agents (norepinephrine or high-dose dopamine) may be required. With abrupt return of peripheral vascular tone, overdoses of other dihydropyridine calcium channel blockers have sometimes progressed to pulmonary edema, and patients must be monitored for this complication.

32. In **NONCLINICAL TOXICOLOGY/Carcinogenesis, Mutagenesis, Impairment of Fertility**, the following text has been added as the first paragraph:

Carcinogenicity and mutagenicity studies have not been conducted with this combination. However, these studies have been conducted with amlodipine and benazepril alone (see below). No adverse effects on fertility occurred when the benazepril:amlodipine combination was given orally to rats of either sex at doses up to 15:7.5 mg (benazepril:amlodipine)/kg/day, prior to mating and throughout gestation.

33. In **NONCLINICAL TOXICOLOGY/Carcinogenesis, Mutagenesis, Impairment of Fertility/** (b) (4), the first paragraph was changed from:

No evidence of carcinogenicity was found when **benazepril** was given, via dietary administration, to rats and mice for 104 weeks at doses up to 150 mg/kg/day. On a body-weight basis, this dose is over 100 times the maximum recommended human dose; on a body-surface-area basis, this dose is 18 times (rats) and 9 times (mice) the maximum recommended human dose. No mutagenic activity was detected in the Ames test in bacteria, in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. At doses of 50-500 mg/kg/day (38-375 times the maximum recommended human dose on a body-weight basis; 6-61 times the maximum recommended dose on a body-surface area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

To:

No evidence of carcinogenicity was found when benazepril was administered to rats and mice for up to two years at doses of up to 150 mg/kg/day. When compared on the basis of body surface area, this dose is 18 and 9 times (rats and mice, respectively) the maximum recommended human dose (calculations assume a patient weight of 60 kg). No mutagenic activity was detected in the Ames test in bacteria, in an *in vitro* test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. At doses of 50-500 mg/kg/day (6-60 times the maximum recommended human dose on a body surface area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

34. In **NONCLINICAL TOXICOLOGY/Carcinogenesis, Mutagenesis, Impairment of Fertility** (b) (4), the first paragraph was changed from:

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of carcinogenicity. For mice, but not for rats, the highest dose was close to the maximum tolerated dose. On a mg/m2 basis, this dose given to mice was approximately equal to the maximum recommended clinical dose. On the same basis, the same dose given to rats was approximately twice the maximum recommended clinical dose.

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

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m2 basis, assuming a 50-kg person).

To:

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 a body surface area basis, similar to the maximum recommended human dose [MRHD] of 10 mg amlodipine/day. For the rat, the highest dose was, on a body surface area 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 body surface area basis).

35. In **NONCLINICAL TOXICOLOGY/Reproductive Toxicity/*Benazapril***, the first paragraph was changed (b) (4)

To:

No teratogenic effects of benazepril were seen in studies of pregnant rats, mice, and rabbits. On a body surface area basis, the maximum doses used in these studies were 60 times (in rats), 9 times (in mice), and about equivalent to (in rabbits) the maximum recommended human dose (assuming a 50-kg woman).

36. In **NONCLINICAL TOXICOLOGY/Reproductive Toxicity/*Amlodipine***, the section was changed (b) (4)

(b) (4)

To:

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 body surface area 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.

37. In **PATIENT COUNSELING INFORMATION/Information for Patients/*Pregnancy***, the passive voice was converted to active voice in the first paragraph. The paragraph now reads:

    Tell female patients of childbearing age that use of drugs like benazepril 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. Tell women using Lotrel who become pregnant to notify their physicians as soon as possible.

38. In the **Patient Package Insert** (PPI), the following information has been added to the end of the insert:

    **Physicians' Desk Reference is a trademark of Thomson Healthcare, Inc. Norvasc® is a registered trademark of Pfizer, Inc. Lotensin® is a registered trademark of Novartis Corp... Eskalith® and Lithobid® are registered trademarks of Noven Therapeutics, LLC.

39. The revision date and version number were updated.

LABELING

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

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)(1)(i)] 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, text for the patient package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 020364/S-047.

LETTERS TO HEALTH CARE PROFESSIONALS

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

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager
(301) 796-3975

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
Text for Patient Package Insert

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20364	SUPPL-47	NOVARTIS PHARMACEUTICALS CORP	LOTREL (AMLODIPIDINE/BENAZEPRIL)CAPSULES

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

/s/

Lori A WACHTER
03/29/2010

NORMAN L STOCKBRIDGE
03/29/2010