DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022081/S-014 **SUPPLEMENT APPROVAL**

Gilead Sciences, Inc.
Attention: Ellen L. Shen, Ph.D.
Associate Manager, Regulatory Affairs
333 Lakeside Dr.
Foster City, CA 94404

Dear Dr. Shen:

Please refer to your supplemental New Drug Application (sNDA) dated June 18, 2010, received June 21, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 and 10 mg Tablets.

We also acknowledge receipt of your amendments dated June 15, July 26, November 3 and 22, 2011, and January 20 and February 8, 2012, and your risk evaluation and mitigation strategy (REMS) assessment dated June 15, 2011.

This Prior Approval sNDA provides for revisions to the labeling and related proposed modifications to the approved REMS for Letairis (ambrisentan).

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. In addition, we have found the REMS assessment to be adequate.

LABELING CHANGES

In the **HIGHLIGHTS** section of the package insert:

Revised text in the **BOXED WARNING**

FROM

LETAIRIS can be prescribed and dispensed only through a restricted distribution program (LETAIRIS Education and Access Program [LEAP]) because of this risk:

- **May cause fetal harm if taken during pregnancy (4.1).**
- **Exclude pregnancy before the start of treatment (2.2).**
- **Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the**

patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed (2.2, 5.1).

TO

- **Do not administer LETAIRIS to a pregnant woman because it may cause fetal harm (4).**
- **Exclude pregnancy before the start of treatment (2.2).**
- **Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed (5.1).**
- **LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). Prescribers, patients, and pharmacies must enroll in the program (5.1)**

Revised text in **DOSAGE AND ADMINISTRATION**

Deleted

- Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests (2.2, 5.1).
- Not recommended in patients with moderate or severe hepatic impairment (2.3, 8.7).

Added

- Tablets should not be split, crushed, or chewed (2.1).

Revised text in **DOSAGE AND ADMINISTRATION**

FROM
5 mg and 10 mg film-coated, unscored tablets (3).

TO
Tablet: 5 mg and 10 mg (3)

Revised text in **CONTRAINDICATIONS**

FROM
Do not administer LETAIRIS to a pregnant woman because it can cause fetal harm (4.1).

TO
Pregnancy

Revised text in **WARNINGS AND PRECAUTIONS**

Deleted
LETAIRIS is available only through a special restricted distribution program (5.1).

Revised text in **ADVERSE REACTIONS**

FROM
Most common placebo-adjusted adverse reactions are peripheral edema, nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain, and constipation (6.1).

TO
Most common adverse reactions (>3% compared to placebo) are peripheral edema, nasal congestion, sinusitis, and flushing (6.1).

Revised text in **USE IN SPECIFIC POPULATIONS**

FROM
- Pregnancy Category X: LETAIRIS is contraindicated in pregnant women (4.1 and 8.1).
- Nursing mothers: Breastfeeding while receiving LETAIRIS is not recommended (8.3).

TO
- Breastfeeding: Choose LETAIRIS or breastfeeding (8.3).
- Not recommended in patients with moderate or severe hepatic impairment (8.7).

Revised text under **RECENT MAJOR CHANGES** to remove outdated text (i.e., text greater than one year old).

Revised the **Table of Contents** to reflect updated labeling text.

In the **FULL PRESCRIBING INFORMATION** section of the package insert:

Revised text in the **BOXED WARNING**

FROM

LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals *[see Contraindications (4.1)].* Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests.

Because of the risk of birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP *[see Warnings and Precautions (5.1)]*.

TO

Do not administer LETAIRIS to a pregnant woman because it may cause fetal harm. LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals *[see Contraindications (4)].*

Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests *[see Warnings and Precautions (5.1)]*.

Because of the risk of birth defects, LETAIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LETAIRIS Education and Access Program (LEAP). As a component of the LETAIRIS REMS, prescribers, patients, and pharmacies must enroll in the program *[see Warnings and Precautions (5.1)]*.

Revised text in **DOSAGE AND ADMINISTRATION**

Added

Healthcare professionals who prescribe LETAIRIS must enroll in the restricted program called LEAP and must comply with the required monitoring to ensure safe use of LETAIRIS *[see Warnings and Precautions (5.1)]*.

FROM
Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*.

TO
Initiate treatment with LETAIRIS in women of childbearing potential only after a negative pregnancy test *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Deleted

2.3 Pre-existing Hepatic Impairment

LETAIRIS is not recommended in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (8.7)]*. There is no information on the use of LETAIRIS in patients with mild hepatic impairment; however, exposure to ambrisentan may be increased in these patients.

Revised text in **DOSAGE FORMS AND STRENGTHS**

FROM
LETAIRIS is available as 5 mg and 10 mg film-coated, unscored tablets.

TO
5 mg and 10 mg film-coated tablets for oral administration

- Each 5 mg tablet is square convex, pale pink, with “5” on one side and “GSI” on the other side.
- Each 10 mg tablet is oval convex, deep pink, with “10” on one sid1 and “GSI” on the other side.

Revised text in **CONTRAINDICATIONS**

FROM
Pregnancy Category X

TO
Pregnancy

FROM
Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed *[see Dosage and Administration (2.2), and Warnings and Precautions (5.1)]*.

TO
Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Revised text in **WARNINGS AND PRECAUTIONS**

FROM

5.1 Prescribing and Distribution Program for LETAIRIS

Because of the risk of birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.
To enroll in LEAP, prescribers must complete the LEAP Prescriber Enrollment and Agreement Form indicating agreement to (see LEAP Prescriber Enrollment and Agreement Form for full prescribing physician agreement):

- Read the Prescribing Information (PI) and Medication Guide for LETAIRIS.
- Enroll all patients in LEAP and re-enroll patients after the first 12 months of treatment and annually thereafter.
- Review the LETAIRIS Medication Guide and patient education brochure(s) with every patient.
- Educate patients on the risks of LETAIRIS, including the risk of teratogenicity *[see Boxed Warning, Warnings and Precautions (5), and Adverse Reactions (6)]*.
- Educate and counsel women of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception–one hormone method and one barrier method, or two barrier methods where one method is the male condom.

Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring.

Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom.

Partner's vasectomy must be used along with a hormone method or a barrier method.

Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure *[see Boxed Warning, Contraindications (4.1)]*.

For women of childbearing potential, order and review a pregnancy test prior to initiation of LETAIRIS treatment and monthly during treatment.

Order and review tests for serum liver enzymes as clinically indicated since some members of this pharmacologic class are hepatotoxic.

Counsel patients who fail to comply with the program requirements.

Notify LEAP of any adverse events or if any patient becomes pregnant during LETAIRIS treatment.

TO

5.1 LETAIRIS Education and Access Program (LEAP)

Because of the risk of birth defects, LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP).
Required components of LEAP:

Healthcare professionals who prescribe LETAIRIS must complete the LEAP Prescriber Enrollment and Agreement Form, enroll in the program, and comply with the REMS requirements.

To receive LETAIRIS, all patients must complete a patient enrollment form and be re-enrolled annually by their prescriber. For women of childbearing potential, (1) a pregnancy test must be ordered and reviewed by the prescriber prior to initiation of LETAIRIS treatment and monthly during treatment, (2) she must agree to be contacted prior to each shipment to confirm that a pregnancy test was completed, (3) she must agree to be counseled on the requirements of the REMS program and the risks of LETAIRIS, and (4) she must agree to be contacted by Gilead if she becomes pregnant while on Letairis or within 30 days of treatment discontinuation.

Pharmacies that dispense LETAIRIS must enroll in the program and agree to comply with the REMS requirements.

Further information is available at www.letairisrems.com or 1-866-664-LEAP (5327).

Revised text in **WARNINGS AND PRECAUTIONS**

Moved the subsection entitled **Pulmonary Veno-occlusive Disease** from 5.5 to 5.3.

Added text in **WARNINGS AND PRECAUTIONS/Hematological Changes**
In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment.

There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion.
Moved text from **ADVERSE REACTIONS/Postmarketing Experience** to **USE IN SPECIFIC POPULATIONS/Hepatic Impairment** (with some modification as noted below)
Elevation of Liver Transaminases
Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure *[See Adverse Reactions (6.2)]*. In patients who develop hepatic impairment after LETAIRIS initiation, the cause of liver injury should be fully investigated. Discontinue LETAIRIS if aminotransferase elevations >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

Minor editorial changes to the text in **ADVERSE REACTIONS/Clinical Trials Experience** that included revising the title of Table 1 (changing the title resulted in elimination of the following events from Table 1: palpitations, nasopharyngitis, abdominal pain, constipation, dyspnea, and headache)

FROM
Adverse Events in >3% of PAH Patients Receiving LETAIRIS and More Frequent than Placebo

TO
Adverse Reactions with Placebo-Adjusted Rates >3%

Revised text in **USE IN SPECIFIC POPULATIONS/Pregnancy**

FROM
Pregnancy Category X [see Contraindications (4.1)].

TO
Pregnancy Category X *[see Contraindications (4)]*. Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using acceptable methods of contraception. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS *[see Warnings and Precautions (5.1)]*.

Revised text in **CLINICAL STUDIES/Long-term Treatment of PAH**

FROM
The long-term follow-up of the patients who were treated with LETAIRIS in the two pivotal studies and their open-label extension (N=383) shows that 95% were still alive at one year and 94% were still receiving LETAIRIS monotherapy. These uncontrolled observations do not allow comparison with a group not given LETAIRIS and cannot be used to determine the long-term effect of LETAIRIS.

TO
In long-term follow-up of patients who were treated with LETAIRIS (2.5 mg, 5 mg, or 10 mg once daily) in the two pivotal studies and their open-label extension (N=383), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 93%, 85%, and 79%, respectively. Of the patients who remained on LETAIRIS for up to 3 years, the majority received no other treatment for PAH. These uncontrolled observations do not allow comparison with a group not given LETAIRIS and cannot be used to determine the long-term effect of LETAIRIS on mortality.

Revised text in **HOW SUPPLIED/STORAGE AND HANDLING**

FROM
LETAIRIS may be prescribed only through the LETAIRIS Education and Access Program (LEAP) by calling 1-866-664-LEAP (5327) or by logging on to www.letairis.com. Adverse events can also be reported directly via this number.
LETAIRIS film-coated, unscored tablets are supplied as follows:

TO
LETAIRIS is available only through the LETAIRIS Education and Access Program (LEAP) by calling 1-866-664-LEAP (5327) or by logging on to www.letairis.com.
LETAIRIS film-coated, tablets are supplied as follows:

Revised text in **PATIENT COUNSELING INFORMATION**

FROM
As a part of patient counseling, doctors must review the LETAIRIS Medication Guide with every patient *[see FDA-Approved Medication Guide (17.5)]*.

17.1 Importance of Preventing Pregnancy

Patients should be advised that LETAIRIS may cause fetal harm. LETAIRIS treatment should only be initiated in women of childbearing potential following a negative pregnancy test.
Women of childbearing potential should be informed of the importance of monthly pregnancy tests and the need to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception–one hormone method and one barrier method, or two barrier methods where one method is the male condom. Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring. Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom. Partner's vasectomy must be used along with a hormone method or a barrier method.
Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Educate and counsel women of childbearing potential on use of emergency contraception for patients whom have had unprotected sex or known or suspected contraceptive failure *[see Warnings and Precautions (5.1)]*.

17.2 Hepatic Effects

Some members of this pharmacological class are hepatotoxic. Patients should be educated on the symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) and instructed to report any of these symptoms to their physician.

17.3 Hematological Change

Patients should be advised of the importance of hemoglobin testing.

17.4 Administration

Patients should be advised not to split, crush, or chew tablets.

17.5 FDA-Approved Medication Guide

*Sections or subsections omitted from the full prescribing information are not listed.

TO
See FDA-approved patient labeling (Medication Guide)
17.1 Letairis Education and Access Program (LEAP)

Advise the patient that LETAIRIS is available only through a restricted program called LEAP.
As a component of LEAP, prescribers must review the contents of the LETAIRIS Medication Guide and the Letairis Patient Enrollment Guide before initiating treatment with Letairis.
Inform the patient that LETAIRIS is available only from Certified Specialty Pharmacies enrolled in LEAP. Provide patients with a list of Certified Specialty Pharmacies.
As a component of LEAP, Certified Specialty Pharmacies must provide a copy of the Medication Guide to patients or caregivers each time LETAIRIS is dispensed. Patients must be instructed to read the Medication Guide each time they receive LETAIRIS because new information may be available. In addition, Certified Specialty Pharmacies must contact patients before each shipment to confirm that the patient will be available to receive the LETAIRIS shipment, and, in the case of women of childbearing potential, to confirm that a pregnancy test has been completed.
Patients must complete a patient enrollment form and be re-enrolled annually by their prescribers using the LEAP Patient Enrollment and Consent form to confirm that they understand the risks of LETAIRIS.
Patients may be asked to participate in a survey to evaluate the effectiveness of LEAP.

17.2 Pregnancy

Instruct patients that the risks associated with Letairis include serious birth defects if used by pregnant women:

- Educate and counsel women of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception: one hormone method and one barrier method, or two barrier methods where one method is the male condom.

- Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring.

- Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom.

- Partner’s vasectomy must be used along with a hormone method or a barrier method.

- Educate and counsel women of childbearing potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure *[see Boxed Warning, Contraindications (4)]*.

Instruct patient to immediately contact their physician if they suspect they may be pregnant.

17.3 Hepatic Effects

Some members of this pharmacological class are hepatotoxic. Patients should be educated on the symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) and instructed to report any of these symptoms to their physician.

17.4 Hematological Change

Patients should be advised of the importance of hemoglobin testing.

17.5 Other Risks Associated with Letairis

Instruct patients that the risks associated with Letairis also include the following:

- Decreases in hemoglobin and hematocrit
- Decreases in sperm count
- Fluid overload

17.6 Administration

Patients should be advised not to split, crush, or chew tablets.

In the **MEDICATION GUIDE**:

Under **What is the most important information I should know about LETAIRIS?**
Added
Your doctor may tell you to use emergency birth control.

Under **What are the possible side effects of LETAIRIS?/Low red blood cell levels**
Added
If this happens, you may need a blood transfusion.

Under **What are the possible side effects of LETAIRIS?/The most common side effects of LETAIRIS are:**
Deleted

- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any 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 request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Letairis (ambrisentan) was originally approved on May 29, 2009, and REMS modifications were approved on July 1 and August 5, 2009, August 24 and October 13, 2010, and March 3, 2011. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of the above revisions to the Medication Guide and revisions to relevant sections of the appended REMS materials, specifically, the Prescriber Guide: Letairis and LEAP Program, and Patient Enrollment Guide to align the content with the above referenced labeling changes.

Your proposed modified REMS, submitted on February 8, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on August 24, 2010.

There are no changes to the REMS assessment plan described in our March 3, 2011 letter.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 22081 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify submissions containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

> **NDA 022081**
> **REMS ASSESSMENT**
>
> **NEW SUPPLEMENT FOR NDA 022081 - PRIOR APPROVAL SUPPLEMENT**
> **PROPOSED REMS MODIFICATION**
> **REMS ASSESSMENT**
>
> **NEW SUPPLEMENT (NEW INDICATION FOR USE)**
> **FOR NDA 022081**
> **REMS ASSESSMENT**
> **PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to 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, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

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

Enclosures:

Package Insert

Medication Guide

Modified REMS

REMS Materials

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
02/15/2012