DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022081/S-017 **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 October 1 and December 15, 2010, and February 22 and March 2, 2011, and your risk evaluation and mitigation strategy (REMS) assessment dated August 11, 2010.

This Prior Approval sNDA provides for revisions to the labeling and 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.

We have determined that the Letairis (ambrisentan) labeling and REMS should be revised in view of new information about the risk of hepatotoxicity with Letairis (ambrisentan). The risk of hepatotoxicity was included in the Letairis (ambrisentan) labeling and the REMS based on experience with other members of the endothelin receptor antagonist class of products, of which Letairis (ambrisentan) is a member. Further evaluation of 12-week controlled clinical study data and post-marketing observational data from the Adverse Event Reporting System (AERS) database has led us to conclude that the rates of liver abnormalities in Letairis-treated patients are consistent with background rates within the general pulmonary arterial hypertension (PAH) population. Furthermore, in controlled trials, the rates of liver abnormalities in Letairis-treated patients were similar to the rates in subjects receiving placebo. Therefore, we agree that the labeling should be revised and the Letairis (ambrisentan) REMS should be modified as described below.

LABELING CHANGES

In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section of the package insert:

Deleted the following text in the **BOXED WARNING**

> **POTENTIAL LIVER INJURY**
> - **Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS and serious liver injury has been reported with related drugs.**
> - **Monitor liver aminotransferases monthly and discontinue LETAIRIS if >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN or by signs or symptoms of liver dysfunction.**

Revised the following text under **INDICATIONS AND USAGE**

FROM

> LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening (1).

TO

> LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%) (1).

Reordered bullets in **WARNINGS AND PRECAUTIONS** and added a new bullet:

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

Revised the following text in **WARNINGS AND PRECAUTIONS**

FROM

> If patients develop acute pulmonary edema during initiation of therapy with LETAIRIS, the possibility of pulmonary veno-occlusive disease should be considered (5.5).

TO

> If patients develop acute pulmonary edema during initiation of therapy with LETAIRIS, consider the possibility of underlying pulmonary veno-occlusive disease and discontinue treatment if necessary (5.5).

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

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

Deleted the following text in the **BOXED WARNING**

> **WARNING: POTENTIAL LIVER INJURY**
> **LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations >3 x ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3 x ULN has been accompanied by bilirubin elevations >2 x ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.**
>
> **In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.**
>
> **Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin >2 x ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.**

And revised the following text in the **BOXED WARNING**

FROM

Because of the risks of liver injury and birth defects…

TO

Because of the risk of birth defects…

Revised the following text under **INDICATIONS AND USAGE**

FROM

LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening (1).

TO

LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%) (1).

Deleted the following text in **DOSAGE AND ADMINISTRATION**

Liver function tests should be measured prior to initiation and during treatment with LETAIRIS *[see Warnings and Precautions (5.1)]*.

Deleted the following text in **WARNINGS AND PRECAUTIONS**

5.1 Potential Liver Injury (see BOXED WARNING)
Treatment with endothelin receptor antagonists has been associated with dose-dependent liver injury manifested primarily by elevation of serum aminotransferases (ALT or AST), but sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferases greater than 3-times the upper limit of normal (>3 x ULN) and total bilirubin >2 x ULN is a marker for potentially serious hepatic injury.

Liver function tests were closely monitored in all clinical studies with LETAIRIS. For all LETAIRIS-treated patients (N=483), the 12-week incidence of aminotransferases >3 x ULN was 0.8% and >8 x ULN was 0.2%. For placebo-treated patients, the 12-week incidence of aminotransferases >3 x ULN was 2.3% and >8 x ULN was 0.0%. The 1-year rate of aminotransferase elevations >3 x ULN with LETAIRIS was 2.8% and >8 x ULN was 0.5%. One case of aminotransferase elevations >3 x ULN has been accompanied by bilirubin elevations >2 x ULN.

Liver chemistries must be measured prior to initiation of LETAIRIS and at least every month thereafter. If there are aminotransferase elevations >3 x ULN and ≤5 x ULN, they should be re-measured. If the confirmed level is >3 x ULN and ≤5 x ULN, reduce the daily dose or interrupt treatment and continue to monitor every two weeks until the levels are <3 x ULN. If there are aminotransferase elevations >5 x ULN and ≤8 x ULN, LETAIRIS should be discontinued and monitoring should continue until the levels are <3 x ULN. LETAIRIS can then be re-initiated

with more frequent measurement of aminotransferase levels. If there are aminotransferase elevations >8 x ULN, treatment should be stopped and re-initiation should not be considered.

LETAIRIS is not recommended in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or increases in bilirubin >2 x ULN, LETAIRIS treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

Revised text in several areas in **WARNINGS AND PRECAUTIONS, Prescribing and Distribution Program for LETAIRIS**

FROM

Because of the risks of liver injury and birth defects…

TO

Because of the risk of birth defects…

FROM

Educate patients on the risks of LETAIRIS, including the risks of hepatotoxicity and teratogenicity *[see Boxed Warning]*.

TO

Educate patients on the risks of LETAIRIS, including the risk of teratogenicity *[see Boxed Warning, Warnings and Precautions (5), and Adverse Reactions (6)]*.

Added

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)]*.

FROM

Order and review liver function tests (including aminotransferases and bilirubin) prior to initiation of LETAIRIS treatment and monthly during treatment.

TO

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

FROM

Notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment.

TO

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

Revised the following text in **ADVERSE REACTIONS**

FROM

See *Boxed Warning* for discussion of potential liver injury and *Warnings and Precautions (5.2)* for discussion of hematological changes.

TO

See *Warnings and Precautions (5.4)* for discussion of hematological changes.

Added the following text in section **6.1 Clinical Trials Experience**

During 12-week controlled clinical trials, the incidence of aminotransferase elevations >3 x upper limit of normal (ULN) were 0% on LETAIRIS and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Liver Function Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x ULN were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on LETAIRIS 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of LETAIRIS to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that LETAIRIS led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that LETAIRIS may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

Deleted the following text in section **6.1 Clinical Trials Experience**

Fewer patients receiving LETAIRIS had adverse events related to liver function tests compared to placebo.

Added the following in section **6.2 Postmarketing Experience**

Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure *[see Adverse Reactions (6.1)]*. Discontinue LETAIRIS if >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

Deleted the term "rapidly" from the first paragraph, third sentence in **CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics**

Ambrisentan is ~~rapidly~~ absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients.

Revised the following text in **CLINICAL STUDIES**

Updated terminology to reflect revisions to the **INDICATIONS AND USAGE** section of the labeling (e.g., changed "idiopathic" to "idiopathic or heritable", changed "exercise capacity" to "exercise ability").

Deleted (but moved to section 6.2) the following text in **CLINICAL STUDIES**

14.3 Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Liver Function Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x upper limit of normal (ULN) were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on LETAIRIS 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients

increasing the dose of LETAIRIS to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that LETAIRIS led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that LETAIRIS may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

Deleted the following text in **HOW SUPPLIED/STORAGE AND HANDLING**

Because of the risk of liver injury and birth defects…

Added the following text in **PATIENT COUNSELING INFORMATION** (section 17.1)

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.

Revised the following text in **PATIENT COUNSELING INFORMATION** (section 17.2)

FROM

17.2 Adverse Liver Effects

Patients should be advised of the importance of monthly liver function testing and instructed to immediately report any symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) to their physician.

TO

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.

Changed all instances of the use of “liver function” or “liver function tests” to “serum liver enzymes” throughout the labeling.

Revised text in **FULL PRESCRIBING INFORMATION: CONTENTS** to reflect the above revisions.

In the **MEDICATION GUIDE**:

Deleted the following text under **What is the most important information I should know about LETAIRIS?**

Possible liver injury.
LETAIRIS can cause liver injury. You must have a blood test to check your liver function before you start LETAIRIS and each month after that. Your doctor will order these blood tests. (See "What are the possible side effects of LETAIRIS?" for information about the signs of liver problems.) Tell your doctor if you have had moderate or severe liver problems, including liver problems while taking other medicines.

Revised the following text under **What is the most important information I should know about LETAIRIS?**

FROM

Women who are able to get pregnant must use two acceptable forms of birth control at the same time, during LETAIRIS treatment and for one month after stopping LETAIRIS. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. **Do not have unprotected sex. Tell your doctor right away if you miss a menstrual period or think you may be pregnant.**

TO

Women who are able to get pregnant must use two acceptable forms of birth control, during LETAIRIS treatment and for one month after stopping LETAIRIS. If you have had a tubal sterilization or have an IUD, these methods can be used alone and no other form of birth control is needed. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. **Do not have unprotected sex. Talk to your doctor or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Tell your doctor right away if you miss a menstrual period or think you may be pregnant.**

Deleted the following bullet under **Who should not take LETAIRIS?**

Your blood tests show possible liver injury.

Deleted the following bullet under **What are the possible side effects of LETAIRIS?**

Possible liver injury. (See "What is the most important information I should know about LETAIRIS?") Call your doctor right away if you have any of these symptoms of liver problems: loss of appetite, nausea, vomiting, fever, unusual tiredness, abdominal (stomach area) pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.

Also, reordered bullets to be consistent with the full prescribing information (e.g., "low red blood cell levels" moved to last in the hierarchy.)

Added the following bullet under **What are the possible side effects of LETAIRIS?**

Some medicines that are like LETAIRIS can cause liver problems. Tell your doctor if you get any of these symptoms of a liver problem while taking LETAIRIS:

- loss of appetite
- nausea or vomiting
- fever
- achiness
- generally do not feel well
- pain in the upper right stomach (abdominal) area
- yellowing of your skin or the whites of your eyes
- dark urine
- itching

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, and August 24 and October 13, 2010. 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 REMS document and 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 March 2, 2011 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.

The revised REMS Assessment Plan should include but is not limited to the following data:

1. reports of operational audits, including results of distribution data reconciliation
2. results of prescriber and patient surveys, including information on patient reported compliance with contraceptive use
3. the total number of patients and female patients of childbearing potential receiving the product
4. drug use patterns (reasons for use, patient demographics, prescribing medical specialties)
5. the number (percent) patient reported compliance with:
    - monthly pregnancy testing for female patients of childbearing potential by quarter and overall
6. reports of pregnancy exposures
7. in the case of pregnancy, the root-cause analysis to determine the reason the REMS failed to prevent the pregnancy exposure
8. the number of pregnancy exposures (pregnancy exposures will be recorded within the REMS database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the REMS database to cases in the global safety database)
9. an analysis of the numbers and reasons for pharmacist calls to prescribers
10. the results of surveys of certified dispensers on the number and type of interactions that occur between pharmacists and prescribers as part of your REMS
11. the frequency of interruptions in therapy, why such interruptions occurred, and, how long any shipment was delayed (e.g., the number of times a shipment was held because the patient had not had their monthly laboratory test)
12. the number and reasons for discontinuation therapy with Letairis (ambrisentan)
13. the frequency and reasons for dispensing >30 day supply
14. a report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24

15. a report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
16. an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified
17. information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

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 you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

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., BCPS, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director of Safety
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/

MARY R SOUTHWORTH
03/03/2011