DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22081/S-012 **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 November 13, 2009, 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 September 15 and October 8, 2010, and your risk evaluation and mitigation strategy (REMS) assessment dated January 8, 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.

LABELING CHANGES

This Prior Approval sNDA provides for the following revisions to the labeling for Letairis (ambrisentan):

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

Added the following text in the beginning of the **BOXED WARNING**

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

Added the following text under **WARNINGS AND PRECAUTIONS**

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

Deleted the following text under **ADVERSE REACTIONS**

Fluid retention was identified as an adverse reaction during postapproval use of LETAIRIS (6.2).

Revised the following text under **DRUG INTERACTIONS**

FROM

No clinically significant interactions of LETAIRIS with warfarin, sildenafil, tadalafil, omeprazole (CYP2C19 inhibitor), ketoconazole (strong CYP3A inhibitor), digoxin, ethinylestradiol, or norethisterone have been observed (7.2).

Other potential interactions are not well characterized, but, based on in vitro data, interactions with P-glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), and uridine 5'-diphosphate glucuronosyltransferases (UGTs) would be expected (7.3).

TO

Multiple dose co-administration of ambrisentan and cyclosporine resulted in an about 2-fold increase in ambrisentan exposure in healthy volunteers. When co-administered with cyclosporine, limit the dose to 5 mg once daily (7).

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:

Added the following text under **WARNINGS AND PRECAUTIONS**

5.5 Pulmonary Veno-occlusive Disease

If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as LETAIRIS, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed LETAIRIS should be discontinued.

Added "nausea and vomiting" to the **ADVERSE REACTIONS/Postmarketing Experience** section of the full prescribing information.

Revised the following text under **DRUG INTERACTIONS**

FROM

7 DRUG INTERACTIONS

7.1 *In vitro* studies

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, uridine 5'-diphosphate glucuronosyltransferases (UGTs), 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of the Organic Anion Transport Protein (OATP), and a substrate but not an inhibitor of P-gp.

7.2 *In vivo* studies

Co-administration of ambrisentan with the following drugs does not result in clinically relevant changes in ambrisentan exposure:

- Ketoconazole
- Omeprazole
- Sildenafil
- Tadalafil

Co-administration of ambrisentan does not change the exposure to the following drugs:

- Warfarin
- Digoxin
- Sildenafil
- Tadalafil
- Ethinyl estradiol/Norethisterone

  In a clinical study in healthy subjects, steady state dosing with ambrisentan 10 mg did not significantly affect the single-dose pharmacokinetics of the ethinyl estradiol or norethisterone components of a combined oral contraceptive (Ortho-Novum 1/35). Based on this pharmacokinetic study, ambrisentan would not be expected to affect significantly the exposure to other estrogen- or progestin-based contraceptives.

7.3 Unknown

The drug interaction potential of ambrisentan is not fully characterized because *in vivo* drug interaction studies have not been conducted with the following types of drugs: strong inducers of CYP3A and 2C19 (rifampin), inducers of UGTs and P-gp (rifampin), strong inhibitors of the transporters P-gp (cyclosporine A) and OATP (cyclosporine A, rifampin, ritonavir). Because ritonavir, cyclosporine A and rifampin can impact the above enzymes and transporters involved in the disposition of ambrisentan, clinically significant changes in the exposure to ambrisentan cannot be excluded.

TO

7 DRUG INTERACTIONS

Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine *[see Clinical Pharmacology (12.3)]*.

Added/revised the following text under **CLINICAL PHARMACOLOGY/ Pharmacokinetics/ Drug Interactions** (to a large extent, the text found previously in **DRUG INTERACTIONS** of the labeling has been moved to this section of the labeling)

***In vitro* studies**
Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of the Organic Anion Transport Protein (OATP), and a substrate but not an inhibitor of P-glycoprotein (P-gp). Drug interactions might be expected because of these factors; however, a clinically relevant interaction has been demonstrated only with cyclosporine *[see Drug Interactions (7)]*. Ambrisentan does not inhibit or induce phase I or II drug metabolizing enzymes at clinically relevant concentrations.

***In vivo* studies**
Effect of other drugs on ambrisentan
The drug interaction potential of ambrisentan has been evaluated using a strong CYP3A inhibitor (ketoconazole), a strong CYP3A and CYP2C19 inducer (rifampin), a CYP2C19 inhibitor (omeprazole), OATP inhibitors (rifampin, cyclosporine), a P-gp, Breast Cancer Resistance Protein (BCRP), OATP1B1, OATP1B3, and CYP3A inhibitor (cyclosporine), a P-gp and UGT inducer (rifampin), and several substrates of CYPs and P-gp.
Cyclosporine: A 14-day repeated dose study in healthy volunteers evaluated the effect of a cyclosporine twice daily regimen (targeting a trough concentration of 150 – 200 ng/mL) on ambrisentan (5 mg once daily) and vice-versa. An about 2-fold increase in the AUC and an about 1.5-fold increase in C_{max} of ambrisentan were observed *[see Drug Interactions (7)]*.
Rifampin: Acute co-administration (3 days) of rifampin (600 mg once daily) was associated with a transient 2-fold increase in the AUC of ambrisentan (10 mg once daily) in healthy volunteers; however, by Day 7, co-administration of rifampin had no clinically relevant effect on AUC or C_{max} of ambrisentan.
Co-administration of ambrisentan with the following drugs does not result in clinically relevant changes in ambrisentan exposure:

- Ketoconazole
- Omeprazole

- Sildenafil
- Tadalafil

Effect of ambrisentan on other drugs
Co-administration of ambrisentan does not change the exposure to the following drugs:

- Cyclosporine
- Warfarin
- Digoxin
- Sildenafil
- Tadalafil
- Ethinylestradiol/Norethindrone

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

In the **MEDICATION GUIDE**:

Added the following text under **Who should not take LETAIRIS?**

Especially tell your doctor if you take the medicine cyclosporine (Gengraf, Neoral, Sandimmune). Your doctor may need to change your dose of LETAIRIS. You should not take more than 5 mg of LETAIRIS each day if you also take cyclosporine.

Deleted the following text under **How should I take LETAIRIS?**

During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

Added the following text under **What are the possible side effects of LETAIRIS?**
Serious side effects of LETAIRIS include:

Low red blood cell levels (anemia) can happen during the first weeks after starting LETAIRIS. Your doctor will do blood tests to check your red blood cells before starting LETAIRIS. Your doctor may also do these tests during treatment with LETAIRIS.

Deleted the following text under **What are the possible side effects of LETAIRIS/The most common side effects of LETAIRIS are:**

Lowering of red blood cell count

Deleted the following text under **What are the possible side effects of LETAIRIS/The most common side effects of LETAIRIS are:**

Allergic reactions (rash, swelling of the face, lips, mouth, tongue, or throat which may cause difficulty in swallowing or breathing) have been reported infrequently.

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. 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 pending "Changes Being Effected" (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.

We request that the revised 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 August 5, 2009 and August 24, 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

materials, specifically, the Prescriber Educational Brochure, Patient Enrollment Guide, and Patient Educational Brochure.

Additionally, in the **Prescriber Educational Brochure** under LETAIRIS Risk Information, the following new section was added:

> 6.1.1
>
> Pulmonary Veno-occlusive Disease
>
> If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as LETAIRIS, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed LETAIRIS should be discontinued.

Your proposed modified REMS, submitted on October 8, 2010 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 May 29, 2009 letter.

We remind you that the requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), 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.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), 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.

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 22081
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 22081-PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22081
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 CDERMedWatchSafetyAlerts@fda.hhs.gov, and 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, PharmD, 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

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
10/13/2010