DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081/S-010

Gilead Sciences, Inc.
Attention: Ms. Hansa Isokoski, MS, RAC
3333 Walnut St.
Boulder, CO 80301-2515

SUPPLEMENT APPROVAL

Dear Ms. Isokoski:

Please refer to your supplemental new drug application (sNDA) dated November 25, 2008, received November 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 and 10 mg Tablets.

We also refer to your amendment dated July 24, 2009 which included proposed revised labeling, a modified Risk Evaluation and Mitigation Strategy (REMS), and a REMS assessment.

This supplemental new drug application provides for the following revisions to the labeling for Letairis (ambrisentan), as well as for modifications to the approved REMS, including the Medication Guide (underlined text for emphasis purposes only):

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

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

- ~~Use caution when LETAIRIS is co-administered with cyclosporine A (5.5 and 7).~~
- ~~Use caution when LETAIRIS is co-administered with strong CYP3A and 2C19 inhibitors (5.6 and 7).~~

Revised the following text under **ADVERSE REACTIONS**

FROM

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

TO

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

Revised the following text under **DRUG INTERACTIONS**

FROM

- No significant interactions of LETAIRIS with warfarin or sildenafil have been observed (7).

TO

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

Revised text under **RECENT MAJOR CHANGES** to reflect the above revisions.

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

Revised the following text under **DOSAGE AND ADMINISTRATION/Pre-existing Hepatic Impairment**

FROM

- LETAIRIS is not recommended in patients with moderate or severe hepatic impairment *[see Special Populations (8.7)]*. Use caution in patients with mild hepatic impairment.

TO

- 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 the last paragraph under **WARNINGS AND PRECAUTIONS/Hematological Changes**

FROM

- Hemoglobin must be measured prior to initiation of LETAIRIS and should be measured at one month and periodically thereafter. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, discontinuation of treatment should be considered.

TO

- Measure hemoglobin prior to initiation of LETAIRIS, at one month, and periodically thereafter. Initiation of LETAIRIS therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing LETAIRIS.

Deleted the following two paragraphs under **WARNINGS AND PRECAUTIONS**

~~**5.5 Co-administration of LETAIRIS and Cyclosporine A**~~

~~Cyclosporine is a strong inhibitor of P-glycoprotein (P-gp), Organic Anion Transport Protein (OATP), and CYP3A4. *In vitro* data indicate ambrisentan is a substrate of P-gp, OATP and CYP3A. Therefore, use caution when LETAIRIS is co-administered with cyclosporine A because cyclosporine A may cause increased exposure to LETAIRIS *[see Drug Interactions (7)]*.~~

~~**5.6 Co-administration of LETAIRIS and Strong CYP3A and 2C19 Inhibitors**~~

~~Use caution when LETAIRIS is co-administered with strong CYP3A inhibitors (e.g., ketoconazole) and CYP2C19 inhibitors (e.g., omeprazole) *[see Drug Interactions (7)]*.~~

Added the following sentence under **ADVERSE REACTIONS/Clinical Trials Experience**

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

Revised the following text under **ADVERSE REACTIONS/Postmarketing Experience**
FROM

The following adverse reaction was identified during postapproval use of LETAIRIS: Fluid retention *[see Warnings and Precautions (5.3)]*.

Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

TO

The following adverse reactions were identified during postapproval use of LETAIRIS: Fluid retention *[see Warnings and Precautions (5.3)]*, heart failure (associated with fluid retention), hypersensitivity (e.g., angioedema, rash), and anemia.

Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Revised the following text under **DRUG INTERACTIONS**
FROM

7 DRUG INTERACTIONS

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A4, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of Organic Anion Transport Protein (OATP). *In vitro* studies show ambrisentan is a substrate but not an inhibitor of P-gp.

The drug interaction potential of ambrisentan is not well characterized because *in vivo* drug interaction studies were not conducted with the following types of drugs: strong inhibitors of CYP3A4 (atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin), and CYP2C19 (omeprazole), strong inducers of CYP3A and 2C19 (rifampin), strong inhibitors of the transporters P-gp (cyclosporine A) and OATP (cyclosporine A, rifampin); and inducers of CYPs, UGTs and P-gp (rifampin). The impact of co-administration of such drugs on ambrisentan exposure is therefore unknown.

7.1 Cyclosporine A

Use caution when LETAIRIS is co-administered with cyclosporine A *[see Warnings and Precautions (5.5)]*.

7.2 Strong CYP3A or 2C19 Inhibitors

Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) or CYP2C19-inhibitors (e.g., omeprazole) *[see Warnings and Precautions (5.6)]*.

7.3 Inducers of P-gp, CYPs, and UGTs

Use caution when LETAIRIS is co-administered with inducers of P-gp, CYPs, and UGTs.

7.4 Warfarin

In healthy volunteers receiving warfarin, daily doses of LETAIRIS (10 mg once daily) did not have a clinically significant effect on prothrombin time (PT), International Normalized Ratio (INR), or the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate).
In patients with PAH receiving warfarin-type anticoagulants, concomitant administration of LETAIRIS did not result in a clinically relevant change in PT, INR or anticoagulant dose. Therefore, no dose-adjustments for warfarin or LETAIRIS are required when co-administered.

7.5 Sildenafil

In healthy volunteers receiving a single dose of sildenafil (20 mg), daily doses of LETAIRIS (10 mg once daily) did not have a clinically relevant effect on the pharmacokinetics of sildenafil or the active metabolite, n-desmethyl sildenafil. Similarly, daily doses of sildenafil (20 mg tid) did not have a clinically relevant effect on the pharmacokinetics of a single dose of LETAIRIS (10 mg). Therefore, no dose-adjustments for sildenafil or LETAIRIS are required when co-administered.

TO

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.

Revised the following text under **USE IN SPECIFIC POPULATIONS/Hepatic Impairment**
FROM

- Use caution when administering LETAIRIS to patients with mild pre-existing impaired liver function who may require reduced doses of LEAIRIS *[see Dosage and Administration (2.3)]*.

TO

- There is no information on the use of LETAIRIS in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients *[see Dosage and Administration (2.3)]*.

Added the following sentence under **OVERDOSAGE**

In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion.

Revised the following text under **CLINICAL PHARMACOLOGY/Pharmacokinetics**
FROM

The absolute bioavailability of ambrisentan is not known. Ambrisentan is rapidly absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients. Food does not affect its bioavailability. *In vitro* studies indicate that ambrisentan is a substrate of P-gp. Ambrisentan is highly bound to plasma proteins (99%). The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well characterized. Based on *in vitro* data, interactions with strong inhibitors of P glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), CYP3A4, CYP2C19, and uridine 5' diphosphate glucuronosyltransferases (UGTs) are possible *[see Drug Interactions (7)]*. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively. Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours.

TO

The pharmacokinetics of ambrisentan (S-ambrisentan) in healthy subjects are dose proportional. The absolute bioavailability of ambrisentan is not known. Ambrisentan is rapidly absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients. Food does not affect its bioavailability. *In vitro* studies indicate that ambrisentan is a substrate of P-gp. Ambrisentan is highly bound to plasma proteins (99%). The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well characterized. In plasma, the AUC of 4-hydroxymethyl ambrisentan accounts for approximately 4% relative to parent ambrisentan AUC. The *in vivo* inversion of S-ambrisentan to R-ambrisentan is negligible. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively. Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours.

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-gp. Drug interactions might be expected because of these factors; however, clinically relevant interactions with drugs utilizing these metabolic pathways have not been demonstrated *[see Drug Interactions (7)]*.

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

In the **MEDICATION GUIDE**:

Revised the following text under **What are the possible side effects of LETAIRIS/Serious side effects of LETAIRIS include:**

FROM

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, right upper stomach pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.

TO

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

Added the following sentence 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.

The following REMS materials were modified as a result of the above labeling changes:

- Revisions to the text in the **REMS Prescriber Enrollment Guide, Patient Enrollment Guide** (For starting therapy with Letairis) and **Patient Education Brochure** (Letairis therapy: What you need to know).

On July 24, 2009, you submitted a REMS modification and REMS assessment for your REMS, last approved on July 1, 2009 (originally approved May 29, 2009). The modified REMS contains the same Medication Guide, elements to assure safe use, implementation system, and timetable for submission of assessments as the original REMS and that approved on July 1, 2009, with the exception of the modifications to the approved REMS listed above.

We have completed our review of this supplemental 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. We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

Your proposed modified REMS is approved and is appended to this letter. The timetable for submission of assessments will remain the same as that approved on May 29, 2009, with the original approval of the REMS.

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

NDA 22-081 REMS ASSESSEMENT

NEW SUPPLEMENT FOR NDA 22-081
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-081
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

CONTENT OF LABELING

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)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-081/S-010**".

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}

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

Enclosure: Agreed-upon 1) Labeling Text (package insert and Medication Guide) and 2) REMS

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
08/05/2009