



NDA 22-081/S-002

Gilead Sciences, Inc.
Attention: Hansa Isokoski, MS, RAC
7575 West 103rd Ave.
Suite #102
Westminster, CO 80021-5426

SUPPLEMENT APPROVAL

Dear Ms. Isokoski:

Please refer to your supplemental new drug application (NDA) dated January 4, 2008 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We also refer to our letter dated November 29, 2007 and your amendment dated February 4, 2008.

This supplemental new drug application provides for the following revisions to the labeling:

1. In the Highlights Section under **Recent Major Changes**, the following text was added:
 - **Warnings and Precautions**, Fluid retention (5.3) 02/2008
 - **Adverse Reactions**, Postmarketing Experience (6.2) 02/2008
 - **Patient Counseling Information**, FDA Approved Medication Guide (17.5) 02/2008

2. In the Highlights Section under **Warnings and Precautions**, the following text was changed

FROM

Mild to moderate peripheral edema (5.3)

TO

Fluid retention may require intervention (5.3)

3. In the Highlights Section under **Adverse Reactions**, the following text was added:
Fluid retention was identified as an adverse reaction during postapproval use of LETAIRIS (6.2).

4. In the Full Prescribing Information: Contents under **Warnings and Precautions**, the following text was changed

FROM

5.3 Peripheral Edema

TO

5.3 Fluid Retention

5. In the Full Prescribing Information: Contents under **Adverse Reactions**, the following text was added:

6.2 Postmarketing Experience

6. In Section 5.3 **Warning and Precautions**, the following text was changed:

FROM

5.3 Peripheral edema

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg LETAIRIS compared to placebo [see *Adverse Reactions (6)*]. Most edema was mild to moderate in severity. If clinically significant peripheral edema develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as heart failure, and the possible need for specific treatment.

TO

5.3 Fluid retention

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg LETAIRIS compared to placebo [see *Adverse Reactions (6)*]. Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients.

In addition, there have been post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting LETAIRIS. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as LETAIRIS or underlying heart failure, and the possible need for specific treatment or discontinuation of LETAIRIS therapy.

7. In Section 6.2 **Postmarketing Experience**, the following text was added:

6.2 Postmarketing Experience

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.

8. In the Letairis (ambrisentan) Medication Guide under **The most common side effects of LETAIRIS are:**”, the following text was changed:

FROM

Swelling of legs and ankles (edema)

TO

Swelling of hands, legs, ankles and feet (peripheral edema) and swelling all over the body (fluid retention)

9. In the RiskMAP Tool – The Prescriber Education Brochure under **LETAIRIS Risk Information**, the following text was added:

Fluid retention

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg LETAIRIS compared to placebo [*see Adverse Reactions (6)*]. Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients.

In addition, there have been post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting LETAIRIS. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as LETAIRIS or underlying heart failure, and the possible need for specific treatment or discontinuation of LETAIRIS therapy.

10. In the RiskMAP Tool – The Prescriber Education Brochure under **LETAIRIS Risk Information – Adverse Reactions**, the following text was changed:

FROM

Placebo-adjusted adverse events in phase 3 clinical trials occurring in $\geq 2\%$ of patients receiving LET AIRIS compared with patients receiving placebo were peripheral edema, nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain, and constipation. Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Peripheral edema was similar in younger patients (<65 years) receiving LET AIRIS (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥ 65 years) receiving LET AIRIS (29%; 16/56) compared to placebo (4%; 1/28).

TO

Placebo-adjusted adverse events in phase 3 clinical trials occurring in $\geq 2\%$ of patients receiving LET AIRIS compared with patients receiving placebo were peripheral edema, nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain, and constipation. Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

11. In the RiskMAP Tool – Patient Education Brochure, entitled “Letairis Therapy: What you need to know” under “**The most common side effects of LETAIRIS are:**”, the following text was changed:

FROM

Swelling of legs and ankles (edema)

TO

Swelling of hands, legs, ankles and feet (peripheral edema) and swelling all over the body (fluid retention)

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

the SPL version of the labeling submitted on February 4, 2008 to the National Library of Medicine for public dissemination.

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

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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., 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

cc: Enclosed Labeling Text

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

/s/

Norman Stockbridge
2/14/2008 12:28:01 PM