



NDA 22-081/S-011

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

SUPPLEMENT APPROVAL

Dear Ms. Isokoski:

Please refer to your supplemental new drug application (sNDA) dated April 16, 2009, received April 17, 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 refer to our supplement request letter dated February 10, 2009, requesting that you make changes to the prescribing information and Medication Guide because we determined that the labeling must be modified to address new safety information to address the risk of testicular toxicity. We also refer to your amendments dated June 9, and June 11, 2009, and to your REMS assessment dated June 19, 2009.

This supplemental new drug application provides for the following revisions to the labeling for Letairis (ambrisentan) and for modifications to the approved Medication Guide and to the approved REMS:

- In the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section of the package insert, the following text under **WARNINGS AND PRECAUTIONS** has been added:

Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (5.4).

- In the **FULL PRESCRIBING INFORMATION** section of the package insert, the following text in **WARNINGS AND PRECAUTIONS** has been added:

5.4 Decreased Sperm Counts

In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were

observed. Based on these findings and preclinical data [*see Nonclinical Toxicology (13.1)*] from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as LETAIRIS have an adverse effect on spermatogenesis.

- Deleted the following text under **Carcinogenesis, Mutagenesis, Impairment of Fertility**:

There are insufficient data on the effects of ambrisentan or other endothelin receptor antagonists on testicular function in man.

The following section of the Medication Guide was modified to achieve consistency with the U.S. Package Insert:

- Changed the following text under the heading **What are the possible side effects of LETAIRIS** in the **Medication Guide**:

FROM

Low sperm count. LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

TO

Sperm Count Reduction. Reduced sperm counts have been observed in some men taking a drug similar to LETAIRIS, an effect which might impair their ability to father a child. Tell your doctor if remaining fertile is important to you.

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

- Revisions to the text in the **REMS Prescriber Education Brochure** and the **REMS Patient Education Brochure (Letairis Therapy: What You Need To Know)**.

On June 9, 2009 and June 19, 2009, respectively, you submitted a REMS modification and REMS assessment for your REMS, approved on May 29, 2009. The modified REMS contains the same Medication Guide, elements to assure safe use, an implementation system, and timetable for submission of assessments as the REMS approved on May 29, 2009, with the exception of the modifications to the approved REMS listed above.

We have completed our review of this 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. Your 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 future 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
< other supplement identification > [if included]
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-008**”.

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

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/

Norman Stockbridge
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