## **CENTER FOR DRUG EVALUATION AND RESEARCH**

## **Approval Package for:**

## **APPLICATION NUMBER:**

## NDA 22-081/S-017

- *Trade Name:* Letairis tablets
- Generic Name: Ambrisentan
- *Sponsor:* Gilead Sciences, Inc.
- Approval Date: March 3, 2011
- *Indications:* 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%).

## CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: NDA 22-081/S-017

## CONTENTS

## **Reviews / Information Included in this NDA Review.**

Approval Letter	X
Approvable Letter	
Labeling	X
Labeling Review	X
Summary Review	
Office Director Memo	
<b>Cross Discipline Team Leader Review</b>	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
<b>Clinical Pharmacology/Biopharmaceutics Review(s)</b>	
<b>Risk Assessment and Risk Mitigation Review(s)</b>	X
Proprietary Name Review(s)	
Other Review(s)	X
Administrative/Correspondence Document(s)	X

## CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: NDA 22-081/S-017

## **APPROVAL LETTER**



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).

ТО

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...

ТО

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).

ТО

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  $\leq$ 5 x ULN, they should be re-measured. If the confirmed level is >3 x ULN and  $\leq$ 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  $\leq$ 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  $>8 \times$  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 xULN 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.

<u>Deleted</u> 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.

## <u>Deleted</u> 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.

ТО

## **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**:

<u>Deleted</u> 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.

<u>Deleted</u> the following bullet under **Who should not take LETAIRIS**? Your blood tests show possible liver injury.

<u>Deleted</u> 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(1)] in structured product labeling (SPL) format, as described at <a href="http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm">http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm</a>, 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/U CM072392.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(1)(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.

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/s/

\_\_\_\_\_

MARY R SOUTHWORTH 03/03/2011

## CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: NDA 22-081/S-017

## **LABELING**

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LETAIRIS<sup>®</sup> tablets safely and effectively. See full prescribing information for LETAIRIS.

LETAIRIS (ambrisentan) tablets Initial U.S. Approval: 2007

#### WARNING: CONTRAINDICATED IN PREGNANCY

See full prescribing information for complete boxed warning. LETAIRIS can be prescribed and dispensed only through a restricted distribution program (LETAIRIS Education and Access Program [LEAP]) because of this risk:

- May cause fetal harm if taken during pregnancy (4.1).
- Exclude pregnancy before the start of treatment (2.2).
- Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed (2.2, 5.1).

#### -----RECENT MAJOR CHANGES------

- Boxed Warning, Potential Liver Injury removal 03/2011
- Warnings and Precautions, Potential Liver Injury removal (5.1) 03/2011
- Warnings and Precautions, Prescribing and Distr bution Program for LETAIRIS (5.1) 03/2011
- Warnings and Precautions, Pulmonary Veno-occlusive Disease (5.5) 10/2010

-----INDICATIONS AND USAGE---

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).

#### -----DOSAGE AND ADMINISTRATION------

- Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated (2.1).
- Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests (2.2, 5.1).
- Not recommended in patients with moderate or severe hepatic impairment (2.3, 8.7).

#### -----DOSAGE FORMS AND STRENGTHS------

• 5 mg and 10 mg film-coated, unscored tablets (3).

#### -----CONTRAINDICATIONS------

• Do not administer LETAIRIS to a pregnant woman because it can cause fetal harm (4.1).

#### -----WARNINGS AND PRECAUTIONS-----

- LETAIRIS is available only through a special restricted distribution program (5.1).
- Fluid retention may require intervention (5.2).
- Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (5.3).
- Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.4).
- 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).

#### -----ADVERSE REACTIONS-----

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

## To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at (1-800-GILEAD5, Option 3) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

#### -----DRUG INTERACTIONS------

 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).

#### -----USE IN SPECIFIC POPULATIONS-------

- Pregnancy Category X: LETAIRIS is contraindicated in pregnant women (4.1 and 8.1).
- Nursing mothers: Breastfeeding while receiving LETAIRIS is not recommended (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Medication Guide).

Revised: 03/2011

Page 1 of 23

#### FULL PRESCRIBING INFORMATION: CONTENTS\* WARNING: CONTRAINDICATED IN PREGNANCY

#### INDICATIONS AND USAGE 1

- 2 DOSAGE AND ADMINISTRATION 2.1 Adult Dosage 2.2 Women of Childbearing Potential
  - 2.3 Pre-existing Hepatic Impairment
- DOSAGE FORMS AND STRENGTHS 3
- CONTRAINDICATIONS 4
- 4.1 Pregnancy Category X
- WARNINGS AND PRECAUTIONS 5
  - 5.1 Prescribing and Distribution Program for LETAIRIS 5.2 Fluid Retention

  - 5.3 Decreased Sperm Counts
  - 5.4 Hematological Changes
  - 5.5 Pulmonary Veno-occlusive Disease

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience 6.2 Postmarketing Experience
- DRUG INTERACTIONS

#### 7 USE IN SPECIFIC POPULATIONS 8

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

- 8.6 Renal Impairment
- 8.7 Hepatic Impairment 10 OVERDOSAGE
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics 13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 14 CLINICAL STUDIES
  - 14.1 Pulmonary Arterial Hypertension (PAH) 14.2 Long-term Treatment of PAH

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

- 17 PATIENT COUNSELING INFORMATION
  - 17.1 Importance of Preventing Pregnancy
  - 17.2 Hepatic Effects
  - 17.3 Hematological Change
  - 17.4 Administration
  - 17.5 FDA-Approved Medication Guide

\*Sections or subsections omitted from the full prescr bing information are not listed.

## FULL PRESCRIBING INFORMATION

## WARNING: CONTRAINDICATED IN PREGNANCY

LETAIRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals [see Contraindications (4.1)]. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests.

Because of the risk of birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP [see Warnings and Precautions (5.1)].

## **1 INDICATIONS AND USAGE**

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%).

## 2 DOSAGE AND ADMINISTRATION

## 2.1 Adult Dosage

Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH).

## 2.2 Women of Childbearing Potential

Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS [see Contraindications (4.1) and Warnings and Precautions (5.1)].

## 2.3 Pre-existing Hepatic Impairment

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

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in patients with mild hepatic impairment; however, exposure to ambrisentan may be increased in these patients.

## **3 DOSAGE FORMS AND STRENGTHS**

LETAIRIS is available as 5 mg and 10 mg film-coated, unscored tablets.

## 4 CONTRAINDICATIONS

## 4.1 Pregnancy Category X

LETAIRIS may cause fetal harm when administered to a pregnant woman. Ambrisentan was teratogenic at oral doses of  $\geq$ 15 mg/kg/day in rats and  $\geq$ 7 mg/kg/day in rabbits; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of LETAIRIS in pregnant women.

LETAIRIS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed [see Dosage and Administration (2.2), and Warnings and Precautions (5.1)].

## **5 WARNINGS AND PRECAUTIONS**

## 5.1 Prescribing and Distribution Program for LETAIRIS

Because of the risk of birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.

To enroll in LEAP, prescribers must complete the LEAP Prescriber Enrollment and Agreement Form indicating agreement to (see LEAP Prescriber Enrollment and Agreement Form for full prescribing physician agreement):

- Read the Prescribing Information (PI) and Medication Guide for LETAIRIS.
- Enroll all patients in LEAP and re-enroll patients after the first 12 months of treatment and annually thereafter.
- Review the LETAIRIS Medication Guide and patient education brochure(s) with every patient.
- Educate patients on the risks of LETAIRIS, including the risk of teratogenicity [see Boxed Warning, Warnings and Precautions (5), and Adverse Reactions (6)].

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- Educate and counsel women of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception–one hormone method and one barrier method, or two barrier methods where one method is the male condom.
  - Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring.
  - Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom.
  - Partner's vasectomy must be used along with a hormone method or a barrier method.
  - 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)].
- For women of childbearing potential, order and review a pregnancy test prior to initiation of LETAIRIS treatment and monthly during treatment.
- Order and review tests for serum liver enzymes as clinically indicated since some members of this pharmacologic class are hepatotoxic.
- Counsel patients who fail to comply with the program requirements.
- Notify LEAP of any adverse events or if any patient becomes pregnant during LETAIRIS treatment.

## 5.2 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.

## **5.3 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.

## **5.4 Hematological Changes**

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with LETAIRIS. These decreases were observed within the first few weeks of treatment with LETAIRIS, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving LETAIRIS in the 12-week placebo-controlled studies was 0.8 g/dL.

Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving LETAIRIS (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis.

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.

## 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.

## **6 ADVERSE REACTIONS**

## 6.1 Clinical Trials Experience

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for LETAIRIS were obtained from two 12-week, placebo-controlled studies in patients with PAH (ARIES-1 and ARIES-2) and four nonplacebo-controlled studies in 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily. The exposure to LETAIRIS in these studies ranged from 1 day to 4 years (N=418 for at least 6 months and N=343 for at least 1 year).

In ARIES-1 and ARIES-2, a total of 261 patients received LETAIRIS at doses of 2.5, 5, or 10 mg once daily and 132 patients received placebo. The adverse events that occurred in >3% of the patients receiving LETAIRIS and were more frequent on LETAIRIS than placebo are shown in Table 1.

	Placebo (N=132)	LETAIRIS (N=261)	
Adverse event	n (%)	n (%)	Placebo-adjusted (%)
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3
Palpitations	3 (2)	12 (5)	3
Nasopharyngitis	1 (1)	9 (3)	2
Abdominal pain	1 (1)	8 (3)	2
Constipation	2 (2)	10 (4)	2
Dyspnea	4 (3)	11 (4)	1
Headache	18 (14)	38 (15)	1

Table 1Adverse Events in >3% of PAH Patients Receiving LETAIRIS and More<br/>Frequent than Placebo

Note: This table includes all adverse events >3% incidence in the combined LETAIRIS treatment group and more frequent than in the placebo group, with a difference of  $\geq$ 1% between the LETAIRIS and placebo groups.

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Few notable differences in the incidence of adverse drug reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving LETAIRIS (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients ( $\geq$ 65 years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously.

The incidence of treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary

arterial hypertension was similar for placebo (7%; 9/132 patients) and for LETAIRIS (5%; 13/261 patients).

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 Serum Liver Enzyme 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.

## 6.2 Postmarketing Experience

The following adverse reactions were identified during postapproval use of LETAIRIS: Fluid retention *[see Warnings and Precautions (5.2)]*, heart failure (associated with fluid retention), hypersensitivity (e.g., angioedema, rash), anemia, nausea, and vomiting.

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.

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.

## **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)].

## **8 USE IN SPECIFIC POPULATIONS**

## 8.1 Pregnancy

Pregnancy Category X [see Contraindications (4.1)].

## 8.3 Nursing Mothers

It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving LETAIRIS is not recommended. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (low, mid, high dose, respectively) the maximum oral human dose of 10 mg on a mg/mm<sup>2</sup> basis.

## 8.4 Pediatric Use

Safety and effectiveness of LETAIRIS in pediatric patients have not been established.

## 8.5 Geriatric Use

In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were  $\geq$ 65 years old and 5% were  $\geq$ 75 years old. The elderly (age  $\geq$ 65 years) showed less improvement in walk distances with LETAIRIS than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

## 8.6 Renal Impairment

The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan *[see Clinical Pharmacology (12.3)]*. Dose adjustment of LETAIRIS in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment.

The impact of hemodialysis on the disposition of ambrisentan has not been investigated.

## 8.7 Hepatic Impairment

The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is *in vitro* and *in vivo* evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan [see Clinical Pharmacology (12.3)]. LETAIRIS is not recommended in

patients with moderate or severe hepatic impairment. 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)].

## **10 OVERDOSAGE**

There is no experience with overdosage of LETAIRIS. The highest single dose of LETAIRIS administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. 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. Massive overdosage could potentially result in hypotension that may require intervention.

## **11 DESCRIPTION**

LETAIRIS is the brand name for ambrisentan, an endothelin receptor antagonist that is selective for the endothelin type-A ( $ET_A$ ) receptor. The chemical name of ambrisentan is (+)-(2*S*)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. It has a molecular formula of C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> and a molecular weight of 378.42. It contains a single chiral center determined to be the (*S*) configuration and has the following structural formula:





Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pKa of 4.0. Ambrisentan is practically insoluble in water and in aqueous solutions at low pH. Solubility increases in aqueous solutions at higher pH. In the solid state ambrisentan is very stable, is not hygroscopic, and is not light sensitive.

LETAIRIS is available as 5 mg and 10 mg film-coated tablets for once-daily oral administration. The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Each square, pale pink LETAIRIS tablet contains 5 mg of ambrisentan. Each oval, deep pink LETAIRIS tablet contains 10 mg of ambrisentan. LETAIRIS tablets are unscored.

## **12 CLINICAL PHARMACOLOGY**

## 12.1 Mechanism of Action

Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes,  $ET_A$  and  $ET_B$ , mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of  $ET_A$  are vasoconstriction and cell proliferation, while the predominant actions of  $ET_B$  are vasodilation, antiproliferation, and ET-1 clearance.

In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH.

Ambrisentan is a high affinity ( $K_i=0.011 \text{ nM}$ ) ET<sub>A</sub> receptor antagonist with a high selectivity for the ET<sub>A</sub> versus ET<sub>B</sub> receptor (>4000-fold). The clinical impact of high selectivity for ET<sub>A</sub> is not known.

## 12.2 Pharmacodynamics

## **Cardiac Electrophysiology**

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either LETAIRIS 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. LETAIRIS 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of LETAIRIS increased mean QTc at  $t_{max}$  by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving LETAIRIS 5-10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

## **12.3 Pharmacokinetics**

The pharmacokinetics of ambrisentan (S-ambrisentan) in healthy subjects are dose proportional. The absolute bioavailability of ambrisentan is not known. Ambrisentan is 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.

## **Drug Interactions**

## 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<sub>max</sub> 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

## **13 NONCLINICAL TOXICOLOGY**

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of up to two years duration were conducted at starting doses of 10, 30, and 60 mg/kg/day in rats (8 to 48 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis) and at 50, 150 and 250 mg/kg/day in mice (28 to 140 times the MRHD). In the rat study, the high and mid-dose male and female groups had their doses lowered to 40 and 20 mg/kg/day, respectively, in week 51 because of effects on survival. The high dose males and females were taken off drug completely in weeks 69 and 93, respectively. The only evidence of ambrisentan-related carcinogenicity was a positive trend in male rats, for the combined incidence of benign basal cell tumor and basal cell carcinoma of skin/subcutis in the mid-dose group (high-dose group excluded from analysis), and the occurrence of mammary fibroadenomas in males in the high-dose group. In the mouse study, high dose male and female groups had their doses lowered to 150 mg/kg/day in week 39 and were taken off drug completely in week 96 (males) or week 76 (females). In mice, ambrisentan was not associated with excess tumors in any dosed group.

Positive findings of clastogenicity were detected, at drug concentrations producing moderate to high toxicity, in the chromosome aberration assay in cultured human lymphocytes. There was no evidence for genetic toxicity of ambrisentan when tested *in vitro* in bacteria (Ames test) or *in vivo* in rats (micronucleus assay, unscheduled DNA synthesis assay).

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of endothelin receptor antagonists in rodents. Testicular tubular degeneration was observed in rats treated with ambrisentan for two years at doses  $\geq 10 \text{ mg/kg/day}$  (8-fold MRHD). Increased incidences of testicular findings were also observed in mice treated for two years at doses  $\geq 50 \text{ mg/kg/day}$  (28-fold MRHD). Effects on sperm count, sperm morphology, mating performance and fertility were observed in fertility studies in which male rats were treated with ambrisentan at oral doses of 300 mg/kg/day (236-fold MRHD). At doses of  $\geq 10 \text{ mg/kg/day}$ , observations of testicular histopathology in the absence of fertility and sperm effects were also present.

## **14 CLINICAL STUDIES**

## 14.1 Pulmonary Arterial Hypertension (PAH)

Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted in 393 patients with PAH (WHO Group 1). The two studies were identical in design except for the doses of LETAIRIS and the geographic region of the investigational sites. ARIES-1 compared once-daily doses of 5 mg and 10 mg LETAIRIS to placebo, while ARIES-2 compared once-daily doses of 2.5 mg and 5 mg LETAIRIS to placebo. In both studies, LETAIRIS or placebo was added to current

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therapy, which could have included a combination of anticoagulants, diuretics, calcium channel blockers, or digoxin, but not epoprostenol, treprostinil, iloprost, bosentan, or sildenafil. The primary study endpoint was 6-minute walk distance. In addition, clinical worsening, WHO functional class, dyspnea, and SF-36<sup>®</sup> Health Survey were assessed.

Patients had idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%), HIV infection (3%), or anorexigen use (1%). There were no patients with PAH associated with congenital heart disease.

Patients had WHO functional class I (2%), II (38%), III (55%), or IV (5%) symptoms at baseline. The mean age of patients was 50 years, 79% of patients were female, and 77% were Caucasian.

## Submaximal Exercise Ability

Results of the 6-minute walk distance at 12 weeks for the ARIES-1 and ARIES-2 studies are shown in Table 2 and Figure 2.

	ARIES-1			ARIES-2		
	Placebo (N=67)	5 mg (N=67)	10 mg (N=67)	Placebo (N=65)	2.5 mg (N=64)	5 mg (N=63)
Baseline	342 ± 73	340 ± 77	342 ± 78	343 ± 86	347 ± 84	355 ± 84
Mean change from baseline	-8 ± 79	23 ± 83	44 ± 63	-10 ± 94	22 ± 83	49 ± 75
Placebo-adjusted mean change from baseline	_	31	51	-	32	59
Placebo-adjusted median change from baseline	_	27	39	-	30	45
p-value†	_	0.008	<0.001	_	0.022	<0.001

## Table 2 Changes from Baseline in 6-Minute Walk Distance (meters)

Mean ± standard deviation

† p-values are Wilcoxon rank sum test comparisons of LETAIRIS to placebo at Week 12 stratified by idiopathic or heritable PAH and non-idiopathic, non-heritable PAH patients



Figure 2 Mean Change in 6-minute Walk Distance

Mean change from baseline in 6-minute walk distance in the placebo and LETAIRIS groups Values are expressed as mean ± standard error of the mean.

In both studies, treatment with LETAIRIS resulted in a significant improvement in 6-minute walk distance for each dose of LETAIRIS and the improvements increased with dose. An increase in 6-minute walk distance was observed after 4 weeks of treatment with LETAIRIS, with a dose-response observed after 12 weeks of treatment. Improvements in walk distance with LETAIRIS were smaller for elderly patients (age  $\geq$ 65) than younger patients and for patients with secondary PAH than for patients

with idiopathic or heritable PAH. The results of such subgroup analyses must be interpreted cautiously.

The effects of LETAIRIS on walk distances at trough drug levels are not known. Because only once daily dosing was studied in the clinical trials, the efficacy and safety of more frequent dosing regimens for LETAIRIS are not known. If exercise ability is not sustained throughout the day in a patient, consider other PAH treatments that have been studied with more frequent dosing regimens.

## **Clinical Worsening**

Time to clinical worsening of PAH was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents or study withdrawal due to early escape. Early escape was defined as meeting two or more of the following criteria: a 20% decrease in the 6-minute walk distance; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. The clinical worsening events during the 12-week treatment period of the LETAIRIS clinical trials are shown in Table 3 and Figure 3.

5					
	ARI	ES-1	ARIES-2		
	Placebo (N=67)	LETAIRIS (N=134)	Placebo (N=65)	LETAIRIS (N=127)	
Clinical worsening, no. (%)	7 (10%)	4 (3%)	13 (22%)	8 (6%)	
Hazard ratio	_	0.28	_	0.30	
p-value, Fisher exact test	_	0.044	_	0.006	
p-value, Log-rank test	_	0.030	_	0.005	

orsening

Intention-to-treat population

Note: Patients may have had more than one reason for clinical worsening. Nominal p-values

There was a significant delay in the time to clinical worsening for patients receiving LETAIRIS compared to placebo. Results in subgroups such as the elderly were also favorable.



Figure 3 Time to Clinical Worsening

Time from randomization to clinical worsening with Kaplan-Meier estimates of the proportions of failures in ARIES-1 and ARIES-2.

p-values shown are the log-rank comparisons of LETAIRIS to placebo stratified by idiopathic or heritable PAH and non-idiopathic, non-heritable PAH patients

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## 14.2 Long-term Treatment of PAH

The long-term follow-up of the patients who were treated with LETAIRIS in the two pivotal studies and their open-label extension (N=383) shows that 95% were still alive at one year and 94% were still receiving LETAIRIS monotherapy. These uncontrolled observations do not allow comparison with a group not given LETAIRIS and cannot be used to determine the long-term effect of LETAIRIS.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

LETAIRIS may be prescribed only through the LETAIRIS Education and Access Program (LEAP) by calling 1-866-664-LEAP (5327) or by logging on to www.letairis.com. Adverse events can also be reported directly via this number.

Package Configuration	Tablet Strength	NDC No.	Description of Tablet; Debossed on Tablet; Size
30 count blister	5 mg	61958-0801-2	Square convex; pale pink; "5" on side 1 and "GSI" on side 2; 6.6 mm Square
30 count blister	10 mg	61958-0802-2	Oval convex; deep pink; "10" on side 1 and "GSI" on side 2; 9.8 mm x 4.9 mm Oval

LETAIRIS film-coated, unscored tablets are supplied as follows:

R only

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP controlled room temperature]. Store LETAIRIS in its original packaging.

## **17 PATIENT COUNSELING INFORMATION**

As a part of patient counseling, doctors must review the LETAIRIS Medication Guide with every patient [see FDA-Approved Medication Guide (17.5)].

## **17.1 Importance of Preventing Pregnancy**

Patients should be advised that LETAIRIS may cause fetal harm. LETAIRIS treatment should only be initiated in women of childbearing potential following a negative pregnancy test.

Women of childbearing potential should be informed of the importance of monthly pregnancy tests and the need to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception–one hormone method and one barrier method, or two barrier methods where one method is the male

Gilead Sciences, Inc.
condom. Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring. Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom. Partner's vasectomy must be used along with a hormone method or a barrier method.

Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. 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 [see Warnings and Precautions (5.1)].

### **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.

### **17.3 Hematological Change**

Patients should be advised of the importance of hemoglobin testing.

### 17.4 Administration

Patients should be advised not to split, crush, or chew tablets.

### **17.5 FDA-Approved Medication Guide**

\*Sections or subsections omitted from the full prescribing information are not listed.

Gilead Sciences, Inc., Foster City, CA 94404

Revised March 2011

LETAIRIS is a registered trademark of Gilead Sciences, Inc. Gilead and the Gilead logo are trademarks of Gilead Sciences, Inc. Other brands noted herein are the property of their respective owners.

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GS22-081-007

# CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 22-081/S-017

# **LABELING REVIEW**

#### **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Division of Drug Marketing, Advertising, and Communications

#### \*\*PRE-DECISIONAL AGENCY MEMO\*\*

Date: November 4, 2010

- To: Daniel Brum Regulatory Project Manager Division of Cardiovascular and Renal Products (DCRP)
- From: Emily Baker Regulatory Review Officer Zarna Patel – Regulatory Review Officer Division of Drug Marketing, Advertising, and Communications (DDMAC)

#### Subject: DDMAC draft labeling comments NDA 022081 LETAIRIS (ambrisentan) Tablets

DDMAC has reviewed the proposed product labeling (PI) and Medication Guide for LETAIRIS (ambrisentan) tablets (Letairis), submitted for consult on October 29, 2010.

The following comments are provided in response to the updated proposed PI and Medication Guide sent via email on October 29, 2010 by Daniel Brum.

We have no additional comments on the proposed Medication Guide at this time.

If you have any questions about DDMAC's comments, please do not hesitate to contact us.

19 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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EMILY K BAKER 11/04/2010

ZARNA PATEL 11/04/2010

## CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: NDA 22-081/S-017

# **RISK ASSESSMENT and RISK MITIGATION REVIEW(S)**

NDA 22081 TSI# 329 REMS and label changes November 2, 2010

#### Medical reviewer's conclusions

I support the proposal to remove the potential liver injury statement from the boxed warning section for Letaris (ambrisentan) tablets. Based upon the results of the clinical trials, the effect of ambrisetan on liver enzyme elevations is similar to that of placebo.

#### Medical reviewer's recommendations

The REMS requirement should be relaxed as requested by the sponsor. The labeling should be changed to reflect this modification.

#### Background

Pulmonary arterial hypertension (PAH) is define as increased pressure in the pulmonary arteries (these arteries carry blood from heart to lungs).

The common early symptoms include shortness of breath during routine activity, fatigue, chest pain, tachycardia The disease is diagnosed when the average pressure in the pulmonary artery is higher than 25 mmHg at rest or 30 mmHg during physical activity (normal is about 15 mmHg at rest). This is measured by right heart catheterization.

The disease severity rating system is shown below.

-Class 1 has no limits to exercise.

-Class 2 has slight or mild limits. You're comfortable while resting, but regular physical activity causes symptoms.

-Class 3 has marked or noticeable limits. You're comfortable while resting. However, walking even one or two blocks or climbing one flight of stairs can cause PH symptoms.

-Class 4 has severe limits. You're not able to do any physical activity without discomfort. You also may have symptoms while at rest.

As the disease progresses the pressure in the arteries continues to rise resulting heart working harder and the right ventricle becoming strained and weak. All physical activity may become limited and heart failure is the most common cause of death.

PAH is split into two categories according to the disease's etiology.

-Primary (idiopathic)

-Secondary pulmonary hypertension

-Connective tissue disorders, such as scleroderma or lupus

-Pulmonary emboli

-Chronic obstructive pulmonary diseases, such as emphysema

-Sleep apnea and other sleep disorders

-Congenital heart disease

-Sickle cell anemia, cirrhosis, AIDS, thyroid disease

-Certain diet medicines and street drugs (such as cocaine).

The currently approved medications probably act by causing vascular smooth muscle dilatation of pulmonary vessels which lower the pulmonary artery pressure and enhances blood flow into the lungs. The drug classes include:

-endothelin receptor antagonists: bosentan (Tracleer), ambrisentan (Letairis)
-phosphodiesterase-5 inhibitors: sildenafil (Revatio), tadalafil (Adcirca)
-prostanoids: iloprost (Ventavis), epoprostenol (Flolan), treprostinil (Remodulin).

Clinical drug trials for PAH are usually 12 weeks in duration. The subjects were patients with PAH, the common etiologies were idiopathic or secondary to connective tissue diseases and with functional class II-III (primarily). The mean age was around 50 years, females were more common than males, and the subjects had been diagnosed with PAH 2-4 years prior to study start. The primary efficacy endpoint is usually submaximal exercise testing (6 minute walk test) with secondary endpoints including clinical worsening, and right heart hemodynamics.

Liver safety monitoring during clinical trials excluded subjects if the subject's AST/ALT > 3 times upper limit of normal (ULN). During the study the following safeguards were instituted:

-increased AST/ALT > 50% above baseline: repeat test;
-increased AST/ALT > 50% above baseline and > 3 times ULN and
-symptomatic: discontinue and follow;
-asymptomatic: continued if < 8 times ULN and follow</li>
-increased AST/ALT > 8 times ULN
-asymptomatic: discontinue (may be restarted if LFTs fall below 3 X ULN).

The results of liver enzyme abnormalities from selected NDAs for PAH are shown below.

Placebo controlled clinical trial data: Endothelin Receptor Antagonists			
	Ambrisentan	Bosentan	(b) (4)
	N=483	N=658	N=1007
AST/ALT	Placebo: 2.3%	Placebo: 2%	Placebo: 5%
>3xULN	Drug: 0.8%	Drug: 11%	Drug: 8%
AST/ALT	Drug 0.2%	Drug: 4%	Drug: 3%
>8xULN			
Bilirubin and	1 subject	2 subjects	12 subjects
aminotransferase			
increases $\geq$ 3xULN			

^not approved in US

Placebo controlled clinical trial data: Phosphodiesterase 5 inhibitors		
	Tadalafil	Sildenafil
	N=323	N=177
AST/ALT >3xULN	Placebo: 2 %	Placebo: 0%
	Drug: 1%	Drug: 1%

Placebo controlled clinical trial data: Prostacyclin Analog		
	Iloprost	
	N=129	
AST/ALT >3xULN	Placebo: 2%	
	Drug: 2 %	

In conclusion, the results of the clinical trials demonstrated that the effect of ambrisetan on liver enzyme elevations was similar to that of placebo.

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/s/

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MARYANN GORDON 11/02/2010

The Evaluation of the Research of the Providence	Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology
Date:	February 15, 2011
To:	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular and Renal Products (DCRP)
Thru:	Claudia Karwoski, Pharm.D. Director, Division of Risk Management (DRISK)
From:	<b>DRISK Scientific Lead</b> Cynthia LaCivita, Pharm.D., Risk Management Analyst (RMA)
	<b>DRISK Review Team</b> Megan Moncur, M.S., RMA, Acting Team Leader Joyce Weaver, Pharm.D., Senior RMA Kathryn O' Connell, M.D., Ph.D., Medical Officer Kate Heinrich, M.A., Health Education Reviewer Sharon Mills, B.S.N., R.N., CCRP, Senior Patient Labeling Reviewer
	<b>Division of Drug Marketing, Advertising and Communications</b> ( <b>DDMAC</b> ) Emily Baker, Pharm.D., Regulatory Review Officer (RRO) Zama Patel, Pharm.D., RRO
Subject:	Interim review of the proposed modification to the Letairis Risk Evaluation
Drug Name(s):	Letairis <sup>TM</sup> (ambrisentan) film coated unscored tablets 5 mg; 10 mg
Therapeutic Class:	Endothelin receptor antagonist (ERA)
Submission Number:	Supplement 17 (Sequence No. 0126)
Application Type/Number:	NDA 22-081 TSI #329
Applicant/sponsor:	Gilead
OSE RCM #:	2010-1478

### 1 PURPOSE

The purpose of this review, performed at the request of the Division of Cardiovascular and Renal Products (DCRP), is to evaluate Gilead's proposed modifications to the Risk Evaluation and Mitigation Strategy (REMS) for Letairis<sup>TM</sup> (ambrisentan). The review focuses on the proposed modifications to the Letairis REMS (NDA 022081) submitted on December 15, 2010 as an amendment to supplement 17. The December 15, 2010 REMS modification supersedes previous REMS submissions in supplement 17.

### 2 BACKGROUND

Letairis was approved with a RiskMAP on June 15, 2007 for the treatment of pulmonary arterial hypertension (PAH); it is the second endothelin receptor antagonist (ERA) to receive FDA approval. Tracleer (bosentan), the first drug in this class, was approved in 2001 with a RiskMAP. The RiskMAP for Tracleer was developed to mitigate hepatotoxicity and teratogenicity. At the time of approval, the teratogenic and hepatic effects were believed to be a class effect of ERAs. Letairis demonstrated teratogenic effects in toxicology studies, however obvious evidence of hepatotoxicity was not observed in preclinical or clinical trials. Under the Food and Drug Administration Amendments Act (FDAAA) of 2007, Letairis was deemed to have in effect an approved REMS. A REMS was officially approved on May 29, 2009 with a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments. The approved REMS is very similar to the RiskMAP that had been in place since initial drug approval.

In February 2009, the sponsor approached the Agency about removing monthly liver testing from the Letairis REMS. In November 2009 and again in June 2010, the sponsor submitted the rationale for removing monthly liver testing from the REMS and submitted a proposed REMS modification.

A CDER Regulatory Briefing was held on October 22, 2010. A review of the data and discussion at this meeting supported the proposal to remove potential liver injury from the boxed warning and modify the REMS accordingly.

Dr. Maryann Gordon's (Medical Officer DCRP) analysis of the clinical trials indicates that Letairis and placebo had a similar effect on elevations in liver enzymes and thereby supports the proposal to remove potential liver injury from the boxed warning. The DRISK review by Dr. Weaver (Review dated Nov 6, 2010) provides a comprehensive summary of the sponsor's safety review, the OND safety review, OSE safety review and relevant medical literature on Letairis and potential liver toxicity. There is agreement among OSE and OND reviewers that clinical trial and post marketing data support the modification to remove monthly liver testing from the labeling and REMS.

### **3 MATERIALS REVIEWED**

The proposed REMS modification submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA).

The following materials were reviewed:

- Proposed REMS modification amendment, Supplement 17, sequence number 0126, December 15, 2010
- Draft labeling dated October 29, 2010, January 5, 2011 and February 8, 2011 (tracked change by DCRP provided via e-mail)
- Mock-up of proposed landing page for Letairis REMS web site (sponsor e-mailed 1/20/2011)

The following materials were referenced:

- Meeting Minutes of the October 22, 2010 Regulatory Briefing on Letairis
- DCRP Review for revision for labeling changes and REMS. Gordan M., dated November 2, 2010
- DRISK REMS Review of the proposal to change liver monitoring requirements in the ambrisentan REMS. Weaver J., dated November 10, 2010

### 4 PROPOSED MODFICATIONS TO THE REMS FOR LETAIRIS

In summary, the sponsor has proposed the following modifications to the REMS based on

(b) (4)

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CYNTHIA L LACIVITA 02/15/2011

CLAUDIA B KARWOSKI 02/15/2011 concur

Evaluation with Research	Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology
Date:	March 3, 2011
То:	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular and Renal Products (DCRP)
Thru:	Claudia Karwoski, Pharm.D. Director, Division of Risk Management (DRISK)
From:	<b>DRISK Scientific Lead</b> Cynthia LaCivita, Pharm.D., Risk Management Analyst (RMA)
	<b>DRISK Review Team</b> Megan Moncur, M.S., RMA, Acting Team Leader Joyce Weaver, Pharm.D., Senior RMA Kathryn O' Connell, M.D., Ph.D., Medical Officer Kate Heinrich, M.A., Health Education Reviewer Sharon Mills, B.S.N., R.N., CCRP, Senior Patient Labeling Reviewer
	<b>Division of Drug Marketing, Advertising and Communications</b> ( <b>DDMAC</b> ) Emily Baker, Pharm.D., Regulatory Review Officer (RRO) Zama Patel, Pharm.D., RRO
Subject:	Final review of the proposed modification to the Letairis Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Letairis <sup>TM</sup> (ambrisentan) film coated unscored tablets 5 mg; 10 mg
Therapeutic Class:	Endothelin receptor antagonist (ERA)
Submission Number:	Supplement 17 (Sequence Numbers 0131 and 0132)
Application Type/Number:	NDA 22-081 TSI #329
Applicant/sponsor:	Gilead
OSE RCM #:	2010-1478

### 1 **PURPOSE**

The purpose of this review is to amend the Division of Risk Management's (DRISK) review (Reviewer: LaCivita February 15, 2011) of Gilead's proposed modification to the Risk Evaluation and Mitigation Strategy (REMS) for Letairis<sup>TM</sup> (ambrisentan).

### 2 DISCUSSION

Comments on the REMS document and all appended REMS materials were still in the process of being finalized when DRISK provided comments for proposed REMS on February 15, 2011. The proposed modification to the Letairis REMS, submitted on February 22, 2011, sequence number 0131, and March 2, 2001, sequence number 0132 addresses all the necessary revisions. The DRISK Review Team finds the proposed modification for the Letairis REMS and the Letairis REMS Supporting Document acceptable.

### **3 RECOMMENDATIONS**

DRISK recommends approval of the Letairis REMS and the following materials.

The complete REMS is attached and includes the following:

	(b) (4)
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CYNTHIA L LACIVITA 03/03/2011

CLAUDIA B KARWOSKI 03/03/2011 concur

# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: NDA 22-081/S-017

# **OTHER REVIEW(S)**



### DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff Office of New Drugs Center for Drug Evaluation and Research Food and Drug Administration Silver Spring, MD 20993 Tel 301-796-0700 FAX 301-796-9744

### Maternal Health Team Review

Date:	November 30, 2010	Date Consulted:	November 18, 2010
From:	Tammie Howard, RN, MSN Regulatory Reviewer, Maternal Health	Team	
Through:	Karen B. Feibus, M.D. Medical Team Leader, Pediatric and M	aternal Health Staff	
	Lisa Mathis, MD Associate Director, Pediatric and Mater	mal Health Staff	
То:	Division of Risk Management (DRISK) Office of Surveillance and Epidemiolog	) gy (OSE)	
Drug:	Letairis (ambrisentan) NDA 22-081/S-	017	
Subject:	Letairis Medication Guide (MG) and R	EMS	
Materials Re	<b>viewed:</b> Sponsor's submitted labeling and Medi	cation Guide.	
Consult Que	stion: Please comment on whether emergency	contraception shou	ld be included in
	patient counseiing for females of child	bearing potential rec	erving Letairis or if

additional revisions are needed regarding pregnancy prevention.

### **INTRODUCTION**

Letairis (ambrisentan), approved by the FDA on June 15, 2007, 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. On May 29, 2009, the Letairis Risk Evaluation and Mitigation Strategy (REMS) was approved and implemented as the Letairis Education and Access Program (LEAP). On June 18, 2010, Gilead Sciences, Inc. submitted a prior approval labeling supplement in which the sponsor proposed to modify the liver monitoring requirements for the REMS, with proposed changes to the Letairis Prescribing information and the Letairis Medication Guide as appropriate.

On October 29, 2010, the Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Risk Management (DRISK) to review the proposed changes for the Medication Guide and the REMS. The Maternal Health Team was consulted by DRISK on November 18, 2010, to comment on whether emergency contraception should be included in patient counseling for females of child bearing potential receiving Letairis or if additional revisions are needed regarding pregnancy prevention. This review includes a review of the sponsor's proposed labeling and Medication Guide, as it pertains to females of childbearing potential receiving Letairis and pregnancy prevention.

### BACKGROUND

Pulmonary Hypertension (PH) is a disease caused by increased pressure in the pulmonary arteries. The disease is classified into 5 groups by the World Health Organization (WHO) and Pulmonary Arterial Hypertension (PAH) belongs to WHO group 1. PAH is a disease in which there is increased, sustained pressure in the pulmonary arteries, which eventually leads to heart failure. The disease becomes progressively worse and may limit all physical activity at some point. Individuals with PAH may develop the disease without a known cause (idiopathic) or as a complication of an underlying disease or condition. Three times as many women as men, between the ages of 20 and 60, develop idiopathic PAH. This age range includes women of childbearing potential with PAH for whom pregnancy is risky and may be fatal<sup>1, 2</sup>. There is no cure for PAH; however, individuals with this disease are often treated with medications to relax and reduce excess cell growth in pulmonary vessels<sup>3</sup>. Endothelin receptor antagonists, such as Letairis (ambrisentan), exert this type of pharmacological effect .

Letairis is indicated for the treatment of pulmonary arterial hypertension. The drug blocks vasoconstriction and cell proliferation in vascular smooth muscle. Although there are no studies of Letairis in pregnant women, in animal studies, Letairis showed teratogenicity in two species (rats and rabbits). In addition, the mechanism of action of endothelin antagonists provides biological plausibility for the teratogenic effects observed in animals. Given the potential for fetal harm if taken by pregnant women, Letairis is contraindicated in pregnancy. The REMS for

<sup>&</sup>lt;sup>1</sup> Website: <u>http://www.nhlbi.nih.gov/health/dci/Diseases/pah/pah\_waht html</u>, National Heart and Lung Blood Institute, National Institutes of Health

<sup>&</sup>lt;sup>2</sup> Charlton, G., Monnery, L., Nanson, J., Primary pulmonary hypertension in pregnancy; a role for novel vasodialtors, British Journal of Anaesthesia, March 2001;87 (2): 295-298.

<sup>&</sup>lt;sup>3</sup> Website: <u>http://www.nhlbi.nih.gov/health/dci/Diseases/pah/pah\_waht html</u>, National Heart and Lung Blood Institute, National Institutes of Health

Letairis requires that women who may become pregnant meet specific requirements for dispensing of drug through specialty pharmacies. The prescribing information and medication guide describe specific contraceptive requirements; however, use of emergency contraception is not addressed.

### **REVIEW OF SUBMITTED MATERIALS**

Sponsor's proposed Warning and Precaution, Patient Counseling Information labeling and Medication Guide

(b) (4)

### **5 WARNINGS AND PRECAUTIONS**

### DISCUSSION/CONCLUSIONS

The Maternal Health Team was consulted to comment on whether information about emergency contraception should be included in patient counseling for females of child bearing potential receiving Letairis and to provide advice on necessary revisions regarding pregnancy prevention. The sponsor's proposed labeling and medication guide provide a warning regarding the contraindication of Letaris use in pregnancy, a warning of potential fetal harm, and a warning to prevent pregnancy. Emergency contraception, while not indicated for routine use as a contraceptive, may prevent pregnancy in the case of unprotected sex or in the case of known or suspected contraceptive failure. Therefore, Letairis labeling and the medication guide should provide information regarding the education and counseling of women of child bearing potential regarding emergency contraception.

During this review, PMHS – maternal health discovered that the information on contraception is inconsistent between the physicians prescribing information and the Medication guide. It appears that when the contraception requirements were updated to allow the use of tubal sterilization and IUDs alone during Letairis use that the addition of this information to the Medication guide did not occur. At this time, this inconsistency should be remedied.

### MHT RECOMMENDATIONS

- 1. Add language addressing emergency contraception to the patient counseling subsection of labeling and medication guide as shown below
- 2. In the medication guide, modify the description of acceptable birth control methods to include the use of tubal sterilization and IUDs as methods that can be used alone.

Provided below are MHT's recommended revisions to the sponsors' proposed labeling and medication guide.

Appendix A of this review provides a tracked changes version of labeling, highlighting the MHT proposed changes.

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TAMMIE B BRENT HOWARD 12/21/2010

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Karen B FEIBUS 12/21/2010 I concur.

LISA L MATHIS 12/21/2010

	Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research Office of Surveillance and Epidemiology Office of Medication Error Prevention and Risk Management
Date:	May 31, 2011
To:	Norman Stockbridge, M.D., Ph.D., Director Division of Cardiovascular and Renal Products (DCRP)
Through:	Mary Willy, Ph.D., Deputy Director Robert Shibuya, M.D., Team Leader Division of Risk Management (DRM)
From:	Jodi Duckhorn, M.A., Senior Social Science Reviewer Division of Risk Management (DRM)
Subject:	DRM Social Science Review of Proposed Methodology and Survey Instruments for the Risk Evaluation and Mitigation Strategy (REMS) Assessment
Drug Name(s):	Letairis (ambrisentan)
Application Type/Number:	NDA 22-081/S-017
Applicant:	Gilead Sciences, Inc.
OSE RCM #:	2010-1478

### **1 INTRODUCTION**

This memorandum provides a review and comments from the Division of Risk Management (DRM) on the proposed methodology and survey instruments that will be used to assess the effectiveness of the Risk Evaluation and Mitigation Strategy (REMS) for Letairis (ambrisentan). Please send these comments to the Applicant within two weeks and copy DRM on the correspondence. Let us know if you would like a meeting to discuss these comments before sending to the Applicant.

### 2 MATERIAL REVIEWED

- May 29, 2009, Letairis REMS and REMS approval letter
- October 6, 2010, DRM review [K.O'Connell] of Letairis REMS assessment
- March 3, 2011, Letairis REMS Modification to remove the risk of hepatotoxicity
- March 15, 2011, Proposed Letairis REMS assessment protocol (methodology and survey instrument) for assessment that is due August 13, 2011

### **3 CONCLUSIONS AND RECOMMENDATIONS**

The following comments are for Gilead Sciences, Inc.:

With regard to the survey of Prescribers:





Please let us know if you have any questions.

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/s/

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JODI M DUCKHORN 05/27/2011

ROBERT B SHIBUYA 05/31/2011

MARY E WILLY 05/31/2011 I concur

## CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: NDA 22-081/S-017

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION			REQUEST FOR CONSU	LTATION	
TO (Division/Office): Mail: OSE cc: Nina Ton		FROM: Dan Brum x60578 DCRP/ODE I			
date October 29, 2010	DATE IND NO. October 29, 2010		NDA NO. 22-081/s-017	TYPE OF DOCUMENT Labeling supplement/REMS modification	DATE OF DOCUMENT June 14, 2010
NAME OF DRUG Letairis (ambrisentan)		PRIORITY C	ONSIDERATION	CLASSIFICATION OF DRUG Endothelin Receptor Antagonist	DESIRED COMPLETION DATE November 12, 2010
NAME OF FIRM: Gilead					
			REASON FO	IR REQUEST	
NEW PROTOCOL       PRI         PROGRESS REPORT       ENI         NEW CORRESPONDENCE       RES         DRUG ADVERTISING       SAI         ADVERSE REACTION REPORT       PAI         MANUFACTURING CHANGE/ADDITION       CO         METTING PLANNED BY       PAI		PRENDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER     FINAL PRINTED LABELING     LABELING REVISION     ORIGINAL NEW CORRESPONDENCE     FORMULATIVE REVIEW     X OTHER (SPECIFY BELOW):		
			II. BIOM	IETRICS	
STATISTICAL EVALUATION BRANC	СН			STATISTICAL APPLICATION BRANCH	
<ul> <li>□ TYPE A OR B NDA REVIEW</li> <li>□ END OF PHASE II MEETING</li> <li>□ CONTROLLED STUDIES</li> <li>□ PROTOCOL REVIEW</li> <li>□ OTHER (SPECIFY BELOW):</li> </ul>		<ul> <li>□ CHEMISTRY REVIEW</li> <li>□ PHARMACOLOGY</li> <li>□ BIOPHARMACEUTICS</li> <li>□ OTHER (SPECIFY BELOW):</li> </ul>			
			III. BIOPHAR	MACEUTICS	
DISSOLUTION     BIOAVAILABILTY STUDIES     PHASE IV STUDIES				<ul> <li>DEFICIENCY LETTER RESPONSE</li> <li>PROTOCOL-BIOPHARMACEUTICS</li> <li>IN-VIVO WAIVER REQUEST</li> </ul>	
			IV. DRUG E	XPERIENCE	
<ul> <li>PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL</li> <li>DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES</li> <li>CASE REPORTS OF SPECIFIC REACTIONS (List below)</li> <li>COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP</li> </ul>			IAGNOSES ROUP	<ul> <li>REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY</li> <li>SUMMARY OF ADVERSE EXPERIENCE</li> <li>POISON RISK ANALYSIS</li> </ul>	
V. SCIENTIFIC INVESTIGATIONS					
				D PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTION	ONS:				
We received a prior approval labeling supplement and REMS modification in June 15, 2010 (amended October 1, 2010) for ambrisentan. We had a regulatory briefing on this sNDA on October 22, 2010.					
The Division is proposing to remove liver toxicity from the boxed warning and has proposed several other related changes to the labeling to reflect general agreement that this drug appears to pose a low risk (if any) for causing liver toxicity. We would like OSE to determine if the medication guide should be revised to reflect our proposed draft changes to the professional labeling DCRP has made some draft revisions to the MG but would greatly appreciate the patient labeling team's input.					
The second key reason for this consult is to ensure that proposed changes to the REMS reflect the proposals in the draft labeling. Cynthia LaCivita explained that she will be reviewing the REMS in consultation with Joyce Weaver.			ges to the REMS reflect she will be reviewing		
I will send Ms. Nina Ton substantially complete prescribing information via email so all parties may complete their reviews. Thanks and please contact me with any questions/conceptor/111			n via email so all any		

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)	□ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER	

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/s/

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DANIEL BRUM 10/29/2010

stor)			
PLETION DATE ek before the wrap-up meeting) 12, 2010			
ISULT .ING			
rmation (SCPI) via			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
Mid-Cycle Meeting: N/A			
Labeling Meetings: TBD (if needed)			
Wrap-Up Meeting: N/A			
HAND			

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/s/

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DANIEL BRUM 10/29/2010

#### MEMORANDUM OF MEETING MINUTES

APPLICATION:	sNDA 022081/S-017
Drug Name:	Letairis (ambrisentan) 5 and 10 mg Tablets
Sponsor:	Gilead Sciences
Type of Meeting:	Regulatory Briefing
Time:	11:00 a.m. – 1:00 p.m. EST
Meeting Chair:	John Jenkins, MD, Director, Office of New Drugs
Meeting Facilitator:	Liz Hespenheide, MSN, RN
Meeting Recorder:	Dan Brum, PharmD, MBA, RAC RPM, Division of Cardiovascular & Renal Products

Regulatory Briefing Panel: (This list may be incomplete.)

Janet Woodcock John Jenkins Curtis Rosebraugh Robert Temple Solomon Sobel Gerald Dal Pan

<u>FDA Presenters:</u> Joyce Weaver, PharmD, BCPS, Senior Drug Risk Management Analyst, DRISK, OSE John Senior, PhD, Senior Drug Risk Management Analyst, OSE Maryann Gordon, MD, Clinical Reviewer, DCRP Mary Ross Southworth, PharmD, Deputy Director of Safety, DCRP

<u>Representatives from Division of Cardiovascular and Renal Products (DCRP):</u> Mary Ross Southworth, PharmD, Deputy Director of Safety Norman Stockbridge, MD, PhD, Director

<u>Representatives from Division of Risk Management (DRISK):</u> Claudia Karwoski, PharmD, Director

FDA Attendees: (See attached sign-in list)

### <u>Topic</u>

Considering changes to the liver monitoring requirements for Letairis (ambrisentan): Implications and potential revisions to the REMS.

### **Meeting Objective**

To determine whether the liver monitoring requirements as imposed by the current REMS should be modified and if so, how should they be changed.

### **Background**

Ambrisentan was the second endothelin receptor antagonist (ERA) approved to treat pulmonary arterial hypertension (PAH). The first agent of the class, bosentan, was approved in 2001 with a RiskMAP to manage hepatic toxicity and teratogenicity. The preclinical development program for bosentan revealed hepatic enzyme elevations and hepatotoxicity (as well as teratogenic and fetotoxic effects). The adverse hepatic effects were confirmed in the controlled clinical trials with bosentan, largely manifested by increases in hepatic transaminases. Despite these toxicities (which were thought to be manageable through careful monitoring), bosentan was approved based on its clear effectiveness in improving symptoms of pulmonary hypertension. Bosentan was the first oral therapy approved for the treatment of pulmonary hypertension.

Both the teratogenic and hepatic effects were thought to be ERA class related, and, indeed, the toxicologic program for ambrisentan revealed similar teratogenic effects. There was, however, little preclinical evidence of hepatotoxicity. Clinical trials also showed no real evidence of hepatotoxicity. Nonetheless, at the time of ambrisentan's 2007 approval, a RiskMAP, nearly identical to that for bosentan, was instituted, linking drug access to patient-reported monthly liver testing and pregnancy testing for females of childbearing potential (FCBP). The RiskMAP was converted to a REMS that was approved in May 2009.

Evaluation of drug-related causes of liver injury for patients taking ERAs is complicated by congestive hepatopathy caused by PAH. In adjudicating causality of potential adverse drug effects in patients with PAH, it is often difficult to distinguish elevated transaminases caused by the ERA from changes caused by worsening PAH and resultant congestive heart failure, hypotension, or reduced blood oxygenation.

In November 2009 the sponsor proposed a change in the REMS to remove monthly liver monitoring based on experience from <sup>(b) (4)</sup> of marketing, with <sup>(b) (4)</sup> patients having received drug for a total of <sup>(b) (4)</sup> patient-years exposure. They based this proposal on data from the controlled clinical trials of ambrisentan, which showed a rate of elevated transaminases indistinguishable from placebo, and a dearth of post-marketing adverse event cases in which ambrisentan could be causally related to liver injury.

#### **Discussion Points**

- In his opening comments, Dr. Jenkins remarked that this may be the first time where the panel has been asked to discuss a modification of an approved REMS to *lessen* the requirements.
- With respect to the clinical trial data presented by Dr. Gordon, Dr. Jenkins asked why the decision was made to require liver monitoring given the clinical trial data did not appear to support such a conclusion. Dr. Gordon responded that there were concerns with two other drugs in the same class, bosentan (approved) and

<sup>(b) (4)</sup> (not approved), so an assumption was made that liver toxicity could be a class effect. Although the NDA data did not suggest an elevated rate of transaminitis, there was relatively limited exposure to the drug.

- Dr. Senior asked if the sponsor had submitted the postmarketing data from the 960 patients in the lab support program to the NDA. Dr. Weaver responded that we reviewed the sponsor's analysis only, and Dr. Senior recommended that we request the raw data. Dr. Southworth noted that postmarketing adverse event cases are generally confounded which makes assessing causality difficult; however, all of the cases of which FDA is aware have been adjudicated thoroughly and there appears to be no "smoking gun".
- Dr. Seeff commented that he had reviewed four AERS cases for evidence of drug induced liver injury (DILI) and ambrisentan did not appear to be the cause in any of the four cases.
- Dr. Temple said the rechallenge data from use in patients with prior ERA-related liver function abnormalities provided a fair amount of reassurance (see section 14.3 of the labeling).<sup>1</sup> Dr. Gordon agreed that this open-label study provided considerable comfort; it would have been even more persuasive had the patients been randomized to ambrisentan or to the drug that was originally associated with transaminase elevations (e.g., bosentan or
- Dr. Jenkins asked if the REMS programs were similar between bosentan and ambrisentan. Dr. Southworth replied yes. Dr. Jenkins said he was surprised that we are not seeing more cases of liver irregularities with bosentan, and commented the similar rates may be a reflection of an effective monitoring program. Dr. Weaver agreed bosentan appeared to have an effective risk mitigation program.

<sup>&</sup>lt;sup>1</sup> In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan,  $(b)^{(4)}$ , 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  $(b)^{(4)}$  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.
- Dr. Jenkins asked why bosentan has far greater market share than ambrisentan. Dr. Southworth speculated that there is a steep learning curve on the part of prescribers and that once prescribers gain familiarity with a particular program, they are reluctant to switch [bosentan was approved in 2001 and ambrisentan was approved in 2007]. She also said that if we believe ambrisentan is safer than bosentan, then we should encourage use of the safer product by making changes to the labeling and REMS to make its liver monitoring less restrictive. Dr. Jenkins noted that <sup>(b) (4)</sup> prescribers have prescribed the drug for about <sup>(b) (4)</sup> patients. Dr. Woodcock said that many practitioners probably do not read labeling carefully; however, prescribers would probably note that both drugs carry similar boxed warnings which could influence prescribing habits.
- Dr. Szarfman performed data mining for bosentan and ambrisentan and noted that bosentan had a higher signal compared to ambrisentan.
- Dr. Temple said that liver monitoring appeared to be helpful because there were few if any fatal liver reactions in patients taking bosentan.
- Dr. Keith Burkhart commented that there are different types of hepatic injury, and also that bosentan and ambrisentan possess different receptor specificities which could account for differing toxicity profiles. Dr. Weaver said that the sponsor has argued that ambrisentan is fundamentally different from bosentan with respect to its
- Dr. Jenkins asked what elements of the Letairis REMS (i.e., in terms of burden on the healthcare system) would continue to be required assuming we approve the sponsor's proposed REMS modification [NDA 22081/S-017]. Dr. Southworth said that for the ~15% of patients that are FCBP, nothing would change; however, for non-FCBPs, we would expect the burden to be reduced substantially. It was noted that the primary components of the REMS would not be affected by the sponsor's proposal; Dr. Weaver said that only the monthly liver testing requirement would be revised.

#### Questions posed to the panel

1. Should the warning about potential liver injury and liver monitoring requirements be removed from the BOXED WARNING section of the labeling for ambrisentan?

#### **Discussion Points**

- Dr. Sobel mentioned that FDA lessened monitoring of liver testing for statins in a step-wise fashion and Dr. Temple said we also did that for the WBC testing requirement for clozapine.
- Dr. Seeff asked how adherent physicians are with the monitoring requirements and whether we know if that makes a difference. Dr. Woodcock explained that physicians are required to perform the monitoring.

- Dr. Rosebraugh asked if there were animal signals for liver toxicity in the ambrisentan development program. Dr. Southworth responded that there were signals for bosentan but not for ambrisentan.
- Dr. Rosebraugh said that the potential for liver toxicity should be removed from the Boxed Warning for the following reasons: 1) There were no significant animal findings, 2) drug classes often do not share toxic effects; several drugs have been known to have benign liver effects even though others in their class have been hepatotoxic 3) the "rechallenge" study provides reassurance, 4) the totality of the data do not indicate a liver problem, and 5)
   (\*) (4) yet has captured the vast majority of market share for this class of drugs.
- Dr. Sobel believed removing the language would be premature.
- There was some discussion as to what FDA would do from a regulatory perspective with regard to <sup>(b) (4)</sup> (not approved) and bosentan (approved). And at what point would FDA act to remove from the market drugs that appeared to be less safe. Dr. Woodcock felt that it would be

Dr. Woodcock thought the totality of the data seem to indicate that the boxed warning should be removed. Dr. Temple asked about changing the bosentan labeling to recommend Dr. Jenkins said recommending such a change would likely take more time – that once the liver toxicity language is removed from the Box Warning for ambrisentan, and if not much changes, then these considerations should be reevaluated.

- Dr. Woodcock expressed concern about the burden imposed by the REMS on patients using the drug.
- Dr. Dal Pan asked if we can learn about all cases of liver toxicity under the REMS. Dr. Weaver said it would be problematic and there would likely be missing information.
- Dr. Dal Pan commented on the striking difference between their usage and he agreed with Dr. Rosebraugh's assessment. That is, relaxing the liver monitoring requirements is appropriate and including a Warning and Precaution would be adequate.
- Dr. Avigan raised the point that, at the time of approval, FDA was managing a potential risk as well as some uncertainty around that risk. But we now have more experience and that when we see reassuring data downstream we should revise the labeling.

(b) (4)

#### **Discussion Points**

- Dr. Senior does not think the sponsor's proposed (b) (4), "
  language is useful. Dr. Jenkins commented that it is probably standard
  language and that these patients would likely get tested if they have
  symptoms (e.g., jaundice).
- Dr. Avigan asked the panel to consider asking the sponsor to perform a study in patients who have abnormalities at baseline and prospectively follow them. He said pre-existing liver disease does not appear to make patients more susceptible to idiosyncratic drug reactions, but if an idiosyncratic drug reaction does occur, that injury might be exacerbated. Dr. Jenkins said such a proposal might be in the form of a PMR.
- Given that many of these patients have underlying liver problems, Dr. Seeff asked what prescribers are expected to do if patients have baseline problems. He said that many believe patients with underlying problems may not be at any higher risk of DILI. Dr. Southworth said that the currently proposed label and REMS calls for

Dr. Senior commented that this is the wrong approach because the drug may benefit patients with elevated liver abnormalities. Furthermore, the drug may improve their liver function as a result of improvement in PAH.

- If the Boxed Warning is updated, Dr. Woodcock suggested trying to gain a better understanding of what happens to patients with baseline liver abnormalities. Dr. Jenkins said excluding patients with baseline abnormalities may be done from the standpoint of the company's liability rather than because of some medical reason. Dr. Temple agreed that we do not know if prior disease makes you more susceptible to problems.
- 3.

#### **Discussion Points**

Dr. Jenkins said that if you answer "yes" to #2, then #3 is implied.

#### 4. If the ambrisentan REMS is changed, what implications might this have for other ERAs?

#### **Discussion Points**

- Dr. Jenkins said that this may have implications for bosentan and for
   (b) (4) where there is a clear signal. Dr. Temple said the bar would indeed be higher for
   (b) (4) under these circumstances.
- Dr. Thompson commented that the risk of hepatotoxicity has been rather different with
   (b) (4) where there have been two fatal cases. Also, there

(b) (4)

have been descriptions in the literature of an atypical (compared to bosentan) pattern of liver injury and recovery where it may take months for recovery. Dr. Jenkins commented that unless (b) (4) can be shown to be better (e.g., more efficacious), then it will probably be difficult to approve this product. Dr. Thompson agreed.

 Ms. Barone voiced concerns over relaxed monitoring and thought a PMR would be helpful in this regard. Dr. Jenkins explained that the previously discussed PMR was related to patients with liver problems at baseline. Dr. Jenkins thought the Division might consider asking the sponsor to follow a subset of such patients to monitor for liver failure.

Attachments:

- Dr. Weaver's Slides
- Dr. Senior's Slides
- Dr. Gordon's Slides
- Dr. Southworth's Slides
- Attendance sheets



### Proposal to Remove Boxed Warning and Mandatory Liver Monitoring from Ambrisentan REMS

CDER Regulatory Briefing October 22, 2010

Reference ID: 2861790



### Background

- Pulmonary arterial hypertension (PAH)
  - PAH 1-yr mortality ~15%
  - PAH can result in liver congestion; liver picture can be confusing for patients receiving hepatotoxic drugs
  - Treatment options limited
- Bosentan first endothelin receptor antagonist (ERA) to receive FDA approval (2001)
  - First po treatment for PAH
  - Had liver injury signal-mandatory liver monitoring included with approval
- Ambrisentan approved in 2007; liver injury thought to be class effect



### Background-2

- Approved with restricted access RiskMAP
  - Teratogenicity (minimize fetal exposure)
  - Hepatotoxicity (minimize hepatotoxicity)
- On FDAAA's list of "deemed" REMS
- REMS approved 5/29/09



### **REMS Elements**

- Medication Guide
- Elements to Assure Safe Use (ETASU)
  - Prescriber certification
  - Pharmacy certification
  - Patient enrollment
  - Monthly monitoring
- Implementation System
- Timetable for Submission of Assessments



# **REMS Monthly Process**

- Patients (or prescribers) called by pharmacy to counsel patients about risks and to ask if monthly lab testing has been completed
  - Liver enzymes
  - Pregnancy testing for females of childbearing potential (FCBP)
- If testing has not been done, prescriber can ok shipment of drug



# Proposal to change liver monitoring

- Sponsor approached FDA Feb 2009 to open talks about removing liver monitoring based on data from marketing
  - FDA advised Sponsor that additional data needed
- Sponsor submitted proposal Nov 2009 based on marketing
  - patients treated average months
     patient-years exposure



# Proposal to change liver monitoring

 Liver chemistries must be measured prior to initiation of LETAIRIS and are recommended after one month of treatment and periodically thereafter as clinically indicated.



## Sponsor's proposal & rationale

- Proposal: Instead of monthly monitoring linked to drug access, liver transaminases measured prior to starting therapy, after 1 month, & then as clinically indicated thereafter
- Rationale:
  - Clinical trial data show ambrisentan to have less effect on liver transaminases than other ERAs
  - Rates of hepatic events in ambrisentan-treated patients are consistent with background rates within the PAH population and are generally attributable to underlying disease or co-morbidities



### Outline

- The Liver in Heart Failure-John Senior, M.D., Associate Director for Science, OSE
- Clinical Trial Data-Maryann Gordon, M.D., Medical Officer, DCRP
- Postmarketing Data-Joyce Weaver, Pharm.D., Risk Management Analyst, DRISK
- Wrap-up-Mary Ross Southworth, Pharm.D., Deputy Director for Safety, DCRP
- Discussion of Options and Questions





# **The Liver in Heart Failure**

John R. Senior, M.D. Associate Director for Science Office of Surveillance and Epidemiology Center or Drug Evaluation and Research

Reference ID: 2861790

 the liver receives about a quarter of the cardiac output, 17-20% or so from portal vein flow from intestinal viscera and another 6-8% from hepatic

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 artery
 mixed portal venous and arterial blood has oxygen extracted from sinusoidal blood; the liver cells remove up to 95%

 centrilobular blood has low oxygen tension as blood leaves liver via hepatic veins to the inferior vena cava and returns to the right auricle–



- the centrilobular zone (3) of the liver is the most vulnerable area to oxygen deprivation

- congestive failure preventing blood egress from, or hypotension reducing blood supply to, may cause liver centrilobular necrosis with very rapid, massive release of enzymes

- pulmonary disease, with low arterial oxygen saturation makes it worse

- and may increase toxicity of drugs such as acetaminophen, others



- leading to "shock liver" (Birgens 1978)
- a.k.a. "ischemic hepatitis" (Bynum 1979)
- -recently "hypoxic hepatitis" (Henrion 2003)
  - is not only "ischemic" (congestion worse)
  - but is not inflammatory, so not "hepatitis"
- maybe best term "hypoxic hepatopathy"
  - very difficult to distinguish from DILI !!



Systemic hypotension or shock alone is less likely to lead to ischemic hepatitis than severe cardiac disease with congestion of the liver. The data lead us to propose that right-sided heart failure with hepatic venous congestion, predisposes the liver to hepatic injury induced by a hypotensive event.

### Seeto et al., Am J Med. 2000;109:109–13



#### Hypoxic Hepatitis

142 cases >>>>	congestive	acute heart	respiratory	circulatory
peak value	failure-80	failure-20	failure-19	shock-19
AST (40 U/L)	15400	11300	6840	15400
ALT (40 U/L)	8590	8590	2900	2775
LDH (200 U/L)	28850	24130	4510	28850
TBL(1.2mg.dL)	22.5	16.7	9.2	22.5
Prothrombin %	8%	9%	6%	11%
Cr (1.2mg/dL)	10.2	10.2	6.7	7.9

Henrion et al. Medicine 2003 Nov;82(6):392-406.

Reference ID: 2861790



Hypoxic liver injury is defined as a massive, but transient, increase in serum transaminase levels due to an imbalance between hepatic oxygen supply and demand in the absence of other acute causes of liver damage. Less often, hypoxic liver injury is seen in patients with severe hypoxemia or septic shock

Characteristically, the transaminase level is elevated 20-fold but normalizes rapidly over several days. Imaging studies reveal hypoechoic or hypodense lesions that resolve completely with reversal of the initiating event. Treatment and prognosis depend on the underlying disease.

#### Ebert EC. Mayo Clin Proc. 2006;81(9):1232-6



Human studies have, until recently, not made any distinction between relative contributions of congestion, hypotension, and hypoxia in causing abnormal liver tests (e.g., elevated alanine, aspartate aminotransferase, alkaline phosphatase, bilirubin, prothrombin time). Also, there are many reports of fulminant "hepatitis" or hepatic failure in the presence of acute congestive heart failure.

Hepatocellular dysfunction is common in the intensive care setting. Over 50% of transient and dramatic elevations of serum aminotransferase elevations have been attributed to hypoxic hepatopathy.

#### Birrer et al. Hypoxic Hepatopathy. Jap Soc Int Med. 2007



Obstructive sleep apnea leads to intermittent hypoxia during sleep, and has been associated with liver injury. Acetaminophen is a widely used drug with known hepatotoxicity. Mice treated with doses of acetaminophen that caused no serum enzyme increases or histologic changes, but mice exposed to hypoxia showed marked increases in serum ALT, AST GGT, TBL and hepatic necrosis. We conclude that hypoxia and acetaminophen treatment lead to synergistic liver injury.

### Savransky et al. Exp Physiol 2008;94(2):228–39.



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Hypoxic hepatitis also known as ischemic hepatitis or shock liver, is characterized by centrilobular liver cell necrosis and sharply increasing serum aminotransferase levels in a setting of cardiac, circulatory, or respiratory failure. Nowadays it is recognized as *the most frequent* cause of acute liver injury with a reported prevalence of up to 10% in the intensive care unit. The main underlying conditions contributing are low cardiac output and septic shock, although a multifactorial etiology is found in the majority of patients. It reverses after successful treatment of the basic circulatory disease.

#### Fuhrmann et al. Wien Klin Woch. 2010;122:129–39



# Bilirubin as a prognostic marker in patients with pulmonary arterial hypertension

variable	hazard ratio	95% C.I.	р
Age, yr	1.01	(0.98-1.04)	0.51
WHO class	4.95	(2.17-11.32)	<0.0001
BNP log pg/dL	2.79	(1.55-5.04)	0.0001
Elevated AST	0.37	(0.05-2.84)	0.34
TBL >1.2mg/dL	13.31	(1.24-18.73)	0.0001

### Takeda et al., BMC Pulm Med. 2010;10:1-18



### take this message home

- in adjudicating causality of adverse drug effects in patients with underlying or acquired heart or pulmonary disease:
- we should take into consideration whether the changes in liver tests were caused by the drug, or by a worsening of congestive failure, hypotension, or reduced blood oxygenation, or all three.
- this applies to pulmonary arterial hypertension !



### **Clinical Trial Data**



## Pulmonary Hypertension

- **Definition**: increased pressure in the pulmonary arteries (these arteries carry blood from heart to lungs).
- Common early symptoms: shortness of breath during routine activity, fatigue, chest pain, tachycardia
- **Diagnosis**: average pressure in the pulmonary artery is higher than 25 mmHg at rest or 30 mmHg during physical activity (normal is about 15 mmHg at rest). This is measured by right heart catheterization.



### Symptom rating

- Class 1 has no limits to exercise.
- Class 2 has slight or mild limits. You're comfortable while resting, but regular physical activity causes symptoms.
- Class 3 has marked or noticeable limits. You're comfortable while resting. However, walking even one or two blocks or climbing one flight of stairs can cause PH symptoms.
- Class 4 has severe limits. You're not able to do any physical activity without discomfort. You also may have symptoms while at rest.



### Prognosis

- Disease Course: pressure in the arteries continues to rise resulting heart working harder and the right ventricle becoming strained and weak. All physical activity may become limited and heart failure is the most common cause of death.
- 1-year mortality approximately 15%



Etiologies

- Primary (idiopathic)
- Secondary pulmonary hypertension
  - Connective tissue disorders, such as scleroderma or lupus
  - Pulmonary emboli
  - Chronic obstructive pulmonary diseases, such as emphysema
  - Sleep apnea and other sleep disorders
  - Congenital heart disease
  - Sickle cell anemia, cirrhosis, AIDS, thyroid disease
  - Certain diet medicines and street drugs (such as cocaine).



### Medical Therapy

- Current medications: probably act by causing vascular smooth muscle dilatation of pulmonary vessels which lower the pulmonary artery pressure and enhances blood flow into the lungs.
  - endothelin receptor antagonists: bosentan (Tracleer), ambrisentan (Letairis)
  - phosphodiesterase-5 inhibitors: sildenafil (Revatio), tadalafil (Adcirca)
  - prostanoids: iloprost (Ventavis), epoprostenol (Flolan), treprostinil (Remodulin)



# Clinical Drug Trials for PAH

- **Duration**: usually 12 weeks
- Subjects: patients with PAH, mostly idiopathic or secondary to connective tissue diseases. Functional class II-III mostly. Mean age is around 50 years, females > males, diagnosed with PAH 2-4 years prior to study start.
- Primary efficacy endpoint: submaximal exercise testing (6 minute walk)
- Secondary endpoints: include clinical worsening, right heart hemodynamics.



### Liver Safety Monitoring During Clinical ERA Trials

- Subjects excluded if AST/ALT > 3 times ULN
- AST/ALT monitored every month
- During study
  - increased AST/ALT > 50% above baseline: repeat test;
  - increased AST/ALT > 50% above baseline and > 3 times ULN and
    - symptomatic: discontinue and follow
    - asymptomatic: continued if < 8 times ULN and follow
  - increased AST/ALT > 8 times ULN
    - asymptomatic: discontinue (may be restarted if LFTs fall below 3 X ULN).



Placebo controlled clinical trial data: Endothelin Receptor Antagonists			
	Ambrisentan	Bosentan	(b) (4)
	N=483	N=658	N=1007
AST/ALT	Placebo: 2.3%	Placebo: 2%	Placebo: 5%
>3xULN	Drug: 0.8%	Drug: 11%	Drug: 8%
AST/ALT	Drug 0.2%	Drug: 4%	Drug: 3%
>8xULN			
Bilirubin and	1 subject	2 subjects	12 subjects
aminotransferase			
increases $\geq$			
3xULN			

^not approved in US



Placebo controlled clinical trial data: Phosphodiesterase 5 inhibitors				
	Tadalafil	Sildenafil		
	N=323	N=177		
AST/ALT >3xULN	Placebo: 2 %	Placebo: 0%		
	Drug: 1%	Drug: 1%		

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Placebo controlled clini	cal trial data: Prostacyclin Analog
	Iloprost
	N=129
AST/ALT >3xULN	Placebo: 2%
	Drug: 2 %

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# Study AMB 222: Ambrisentan in subjects who previously d/c'd ERA therapy due to Increased LFT's

#### Table 10.4 Previous ERA Use and Associated LFT Elevations (Population: All Subjects)

		Total		
		N = 36		
LFT Elevations	Bosentan	(b) (4)	First ERA Failure*	
Subjects Who Discontinued ERA, n	34	5	36	
Subjects With AST >3xULN, n (%)	32 (94.1)	4 (80.0)	33 (91.7)	
Subjects With AST >5xULN, n (%)	21 (61.8)	4 (80.0)	24 (66.7)	
Subjects With ALT >3xULN, n (%)	28 (82.4)	5 (100.0)	32 (88.9)	
Subjects With ALT >5xULN, n (%)	10 (29.4)	3 (60.0)	13 (36.1)	
Subjects With Total Bilirubin >2xULN, n (%)	1 (2.9)	0 (0.0)	1 (2.8)	
Duration on ERA Before Discontinuation, weeks,				
Median	13.9	28.7	15.6	
Min, Max	4, 141	17.6, 53.6	4, 141	



# Ambrisentan in patients with previous ERA-related liver abnormalities

- 36 patients who previously discontinued ERA therapy for liver abnormalities
  - 8 patients had been rechallenged with bosentan. All 8 had recurrence of increased transaminases requiring bosentan discontinuation.
- Before ambrisentan initiation, AST/ALT normalized



# Ambrisentan in patients with previous ERA-related liver abnormalities

- Median follow-up 13 weeks
- No patients discontinued treatment with ambrisentan for aminotransferase elevations
  - 50% increased dose to 10 mg
  - One patient developed mild aminotransferase elevations, dose was decreased to 2.5 mg and abnormality resolved. Dose subsequently increased to 10 mg with no recurrence



### **Overview of Postmarketing Data**

- REMS report
  - Use data-patients, prescribers
  - Discontinuation reasons
- Data from lab support program
- Ongoing non-US observational study
- Adverse event reports
  - PSUR/other sponsor submissions
  - AERS



(b) (4)

#### Use Data-Patients\*

#### US patients (total US patient exposure





\*data from ambrisentan REMS Report 8/2010



# **Use Data-Prescribers\***



(b) (4)

- Pulmonologists-
- Cardiologists-
- Rheumatologists-
- Internist-
- Other or unspecified-



### **Discontinuation reasons\***

(b) (4)

 Cumulatively, of patients who received at least one shipment of ambrisentan discontinued ambrisentan therapy

(b) (4)

- Physician choice-
- Patient deceased-
- Patient choice-
- Liver AE-
- Insurance-

\*data from ambrisentan REMS report 8/2010, reason cited by prescriber



# Lab support program

- Sponsor-supported program to coordinate lab testing
- Patients can opt to use the sponsor's lab support program or they can get their testing using their usual laboratory
- For patients who opt in to the lab support program, it is possible to link lab results, action taken in response to lab results, & outcome

## Data from lab support program

- As of 9/23/2009, 960 patients were actively participating in the lab support program, with 4 (median) blood draws per patient (range, 1-19).
- Sixteen patients (1.7%) had an elevation of liver transaminases > 3 X ULN.
  - 11/16 had an increase in liver transaminases that resolved on the next test; in all 11 cases, ambrisentan was continued or successfully restarted
  - 1 patient had persistent stable increased liver transaminases, but continued on ambrisentan



### Data from lab support program-2

- 2 patients had elevation of liver transaminases > 8 X ULN; both patients had other underlying reasons that likely contributed (congestive liver hepatopathy; hep C)-ambrisentan D/Ced & not restarted
- 1 patient had both liver transaminases > 3 X ULN and tbili > 2 X ULN; this patient with sickle cell disease has continued ambrisentan with resolution of the elevated aminotransferases and cont' elevated bili
- 1 patient recd liver transplant & no longer needed ambrisentan (hx hep C & ETOH abuse)
- Sponsor's conclusion from lab support program: no serious liver injury 2° ambrisentan was identified 42



# **Observational Study**

- Purpose of the study-In order to increase the size of the human safety database and to supplement routine pharmacovigilance activities, GSK is implementing a postmarketing surveillance programme for ambrisentan, called VOLT (VOLibris Tracking). This programme will collect observational data to more fully characterize hepatic safety as well as the overall safety profile of ambrisentan when used in clinical practice. Will recruit 800 subjects from 80 locations in AUS, CA, and EU
- Collecting exposure data, AE data
- Targeted to be completed December 2012
- After ~ 450 enrolled, 4 notable liver AEs



# **Observational Study-2**

- A 44-year-old male developed asymptomatic hepatitis 2 months after starting treatment with ambrisentan 5mg, which may have been due to a hypersensitivity reaction, auto-immune disease or viral hepatitis based on liver biopsy results; resolved w/ dechallenge; pt previously had experienced increased liver transaminases w/ bosentan and
- A 27-year-old female with a history of two liver transplants, chronic transplant rejection and cryptogenic cirrhosis of the liver developed increased transaminases 17 days after starting ambrisentan 5mg and 13 days after last dose; event resolved



### OSE assessment of VOLT cases

 Both patients had underlying hepatic processes; however, it is possible that ambrisentan contributed to the events



### Summary of Post-marketing Hepatic AEs\*

- 127 reports of liver injury (120 spontaneous + 7 in clinical trials)
- 6 cases had liver transaminases > 3 X
   ULN, & t. bili > 2 X ULN

– Possible alternative causes for all 6 cases

from sponsor's 1/18/2010 submission, Revised Review of Post-Marketing Hepatic Adverse Event Data (2 Years)



#### Possible other causes for 6 cases

- sickle cell disease in a patient with elevated baseline serum total bilirubin 7.7 (2008-0015335);
- suspected gall bladder disease in a patient who developed increased serum total bilirubin (5 x ULN) and alkaline phosphatase (3.3 x ULN) 11 days before an increase in ALT to 3.1 x ULN (2009-0019707);
- documented cardiogenic shock and right sided heart failure due to underlying PAH (2009-0021875)



#### Possible other causes for 6 cases

- underlying portopulmonary hypertension and abrupt withdrawal of treprostinil in a patient with cirrhosis of the liver secondary to chronic hep C infection and hepatocellular carcinoma status post chemoembolization (2008-0018822)
- underlying hep C and stage 4 alcoholic cirrhosis (2008-0019372);
- concurrent right heart failure, diagnosed after the patient admitted missing several doses of ambrisentan and 3-4 days of sildenafil and furosemide and with a baseline serum total bilirubin of 1.7 x ULN (2008-0016633; clinical study report)



#### Summary of Action Taken with Ambrisentan in 120 Postmarketing Liver Toxicity Cases

Sponsor-submitted data from 1/18/2010 submission

Action taken	Number of Cases			
Drug discontinued	65			
Dosage maintained	16 (hepatic event resolved in 6 cases)			
Drug interrupted	14			
Dose reduced	6 (Hepatic event resolved in 4 cases)			
Unknown	19			



#### Summary of Outcomes in Postmarketing Liver Toxicity Cases (n=48)

Sponsor-submitted data from 1/18/2010 submission; outcome not known in 72 cases

Outcome	Number of Cases
Recovered/resolved	20
Recovered/resolved with sequelae	3
Recovering/resolving	4
Not recovered/not resolved	10
Fatal	11
Non-hepatic (MI, anemia, pneumonia, MOF after bone marrow transplant, worsening pulmonary hypertension, shock)	6
Hepatic (liver cancer, complications of cirrhosis and renal failure, failure of liver transplant, end-stage liver disease, cirrhosis, pleuropericardial effusion, sclerotic bowel)	5



# Liver Injury Reports by Exposure

- 120 spontaneous reports of liverassociated adverse events
  - patient-years exposure
  - events per patient-years exposure
- Consistent with expected background incidence in patients w/ PAH (data from placebo arms of ERA clinical trials)

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## Letairis (ambrisentan) and Tracleer (bosentan) Liver failure reports in AERS

Susan Lu, SE Team Leader & Allen Brinker, M.D., Medical Officer Division of Pharmacovigilance I OSE / CDER



# Overview of domestic AERS data for bosentan and ambrisentan

	Bosentan	Ambrisentan
	(2002-2010)	(2007-2010)
Total count	4362	2041
Serious	3698	2023
Death	1470	775
Hepatobiliary SOC	654 (15% of total reports)	<b>73 (3.6% of</b> total reports) <sup>53</sup>

Reference ID: 2861790



#### AERS search strategy for liver failure

#### MedDRA terms

- HLT Hepatic failure and associated disorders
- PT Hepatic necrosis
- PT Hepatitis fulminant
- PT liver transplant
- Limited to domestic, serious and reports received after date of ambrisentan approval (June 15, 2007- May 5, 2010)



# AERS results for liver failure related events (6/15/07-5/6/10)

- Ambrisentan: 13 reports
  - 6 deaths
  - Represents 0.7% of all reports \*
- Bosentan: 22 reports
  - 15 deaths
  - Represents 3.1% of all reports\*

\*based on total domestic reports received 6/15/07- 5/6/10 for Bosentan (702) and Ambrisentan (1948)



## AERS reports of liver failure for Bosentan (n=22)

- 16 exclusions- alternative causes (8), lack of temporal relationship (5), liver transplant unrelated to drug (2), LFTs elevation (1)
- 3 cases unassessable due to lack of information
- 3 liver failures possibly related to Bosentan
  - 2 deaths but cannot conclude relationship to bosentan



# AERS reports of liver failure for ambrisentan (n=13)

- 11 exclusions- pre-existing liver dysfunction (5), alcohol abuse (2), cardiac related (2), sepsis with bone marrow transplant (1), other suspect drugs/negative RC w ambrisentan (1)
- 1 case unassessable due to lack of info
- 1 case possibly attributed to ambrisentan
  - 52-year-old pt died; decompensated heart failure and hypotension might have contributed to the event



## Summary

- 4 liver failure reports in AERS with bosentan (3) and ambrisentan (1) for period of ambrisentan marketing
- Crude marketing data show that use mirrors liver failure (bosentan 3-4: ambrisentan 1)
- Assessment of hepatic events in PAH may be confounded in patients with right heart failure and hepatic congestion



Wrap-up

- The Liver in Heart Failure-John Senior Difficult to distinguish drug-induced hepatotoxicity from hypoxic hepatopathy
- Clinical Trial Data-Maryann Gordon Ambrisentan-related liver toxicity low in clinical trials
- Postmarketing Data-Joyce Weaver
   No smoking gun yet in postmarketing data



## Wrap-up

- Ambrisentan was approved with a RiskMAP/REMS because hepatotoxicity (and teratogenicity) was thought to be a ERA-class associated effect
- Bosentan, the first oral ERA therapy approved, demonstrated a convincing safety signal for hepatotoxicity in the preclinical and clinical development program.



# Wrap-up: Clinical Trials

- RCTs of drug therapy in PAH:
  - Placebo rate of *AST/ALT*'s approximately 2%

– Ambrisentan rate: 0.8%

 Small (n=36) switching study showed ambrisentan can be tolerated by those with bosentan or related liver injury



# Wrap-up: Post-marketing

- Difficult to definitively attribute liver injury to ERA therapy because of underlying or concomitant disease/medication
- Hard to ascertain whether tests were clinically indicated or part of routine monitoring
- Exposure to ambrisentan is small

   — 
   patient-years in US



# Wrap-up: Post-Marketing

- Structured Programs
  - Incidence of  $\uparrow$ ALT/AST'ss 0.8 to1.7%
  - Majority resolved with continued therapy
  - In many cases, liver injury could be attributed to other causes
- "Spontaneous" reporting
  - PSUR: events/ patient years
  - AERS: 13 cases of liver failure
    - 11 with alternative causes
    - 1 unassessable
    - 1 possible case (with decompensated HF and APAP use reported)



### Wrap-up

- Clinical Trial data are reassuring
- Post-marketing data often confounded, but no "smoking gun" case



#### Sponsor's proposal

Remove "Potential Liver Injury" from the Boxed Warning

 — "moves to Warnings and

Precautions

- (b) (4)
- REMS changes





#### **Options for liver testing within ambrisentan REMS**





#### **Options for liver testing within ambrisentan REMS**





#### **Options for liver testing within ambrisentan REMS**




## **Options for liver testing within ambrisentan REMS**





## **Options for liver testing within ambrisentan REMS**





# Questions

1. Should the warning about potential liver injury and liver monitoring requirements be removed from the **BOXED WARNING** section of the labeling for ambrisentan?



# Questions





# Questions







# **Back-up slides**



# Shipment delays\*



\*data from ambrisentan REMS report 8/2010



## Figure 1

### Age and Gender Profile of Post-Marketing Spontaneous Hepatic Cases

(b) (4)



(b) (4)

### Figure 2 Age and Gender Profile of Patients in LEAP (15 June 2007 – 14 June 2009)





(b) (4)

### Figure 3

### Time to Onset of Hepatic Events in Post-Marketing Spontaneous Hepatic Cases (n=44)



# Liver failure report with possible association with ambrisentan

A 52-year-old woman with pulmonary arterial hypertension began ambrisentan (dosage unknown) in February 2009. Concomitant medications included warfarin, digoxin, magnesium salicylate, beclomethasone, Atrovent, and folic acid. The patient had systemic sclerosis, interstitial lung disease (ILD), Class IV PAH and was in remission from lymphoma.



# Liver failure report with possible association with ambrisentan

The patient's vital signs at her last clinic visit were blood pressure (BP) 120/70, heart rate (HR) 110 and respiratory rate (RR) 20. She also had lost a lot of weight and was confined to a wheelchair. The patient had Velcro crackles half way up. Her liver function tests on May 22, 2009 were t: ALT 37, AST 22, total bili 0.5 and ALP 118. Virus serologies for hepatitis A/B/C, Epstein-Barr virus and cytomegalovirus were negative.



# Liver failure report with possible association with ambrisentan

On an unknown date, the patient was admitted with weakness for 4-5 days and found to have liver function test in 1000's. The patient's liver function tests June 7, 2009 were ALT 1388, AST 1471, total bilirubin 2.0 and ALP 123 (units and normal range not specified). Ambrisentan was discontinued. The treating physician believed that the use of Percocet (extent of use not reported), decompensated heart failure, and hypotension contributed to the abnormal liver function tests. The patient then developed encephalopathy, coagulopathy and she died

## **Regulatory Briefing Meeting:**

Title: Considering changes to the liver monitoring requirements for Letaris (ambrisentan): implications and potential revisions to the REMS

## DATE: 10/22/10

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DANIEL BRUM 11/09/2010

/s/

MARY R SOUTHWORTH 11/09/2010



Food and Drug Administration Silver Spring MD 20993

#### NDA 22081

### **GENERAL ADVICE**

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 New Drug Application (NDA) 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 your submission dated March 15, 2011 which included revisions to the Letairis Knowledge Attitude and Behavior (KAB) and Pregnancy Root Cause Analysis (PRCA) survey methodologies.

We have completed our review of your submission and we have the following comments:

### With regard to the survey of Prescribers:



#### With regard to the survey of Patients and Caregivers:





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 for Safety Division of Cardiovascular and Renal Products Office of Drug Evaluation I Center for Drug Evaluation and Research

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/s/

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MARY R SOUTHWORTH 06/14/2011