

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022081Orig1s039

Trade Name: LETAIRIS

Generic or Proper Name: ambrisentan

Sponsor: Gilead Science Inc.

Approval Date: 03/28/2019

Indication: Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group):

- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022081Orig1s039

APPROVAL LETTER



NDA 022081/S-039

SUPPLEMENT APPROVAL

Gilead Sciences, Inc.
Attention: April Given
Manger, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Givens:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 5, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Letairis (ambrisentan) 5 mg and 10 mg Tablets.

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Letairis risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Letairis was originally approved on October 29, 2009, and the most recent REMS modification was approved on November 30, 2018. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS establishes a Single Shared System (SSS) REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Letairis and ANDAs referencing Letairis, called the Ambrisentan REMS Program.

Your proposed modified REMS, submitted on December 5, 2017, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised. Submit REMS Assessments annually from the date of the initial REMS approval (03/28/2019). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Submit each assessment so that it will be received by the FDA on or before the due date.

The revised REMS assessment plan must include, but is not limited to, the following:

1. **REMS Program Utilization (for each reporting period and cumulatively)**
 - a. Prescribers
 - i. Number of certified prescribers, and the number and percentage of enrolled health

- care providers who have prescribed Ambrisentan stratified by medical specialty
- b. Pharmacies
 - i. Number of certified pharmacies by pharmacy type (inpatient and outpatient)
- c. Patients
 - i. Number and percentage of enrolled patients by patient type:
 - 1) Females of reproductive potential (FRP)
 - 2) Pre-pubertal females (as classified on the Ambrisentan REMS Program Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form)
 - 3) Females of non-reproductive potential (FNRP)
 - ii. Number of patients, new and total, by patient type grouped by the following age ranges
 - 1) < 6
 - 2) 6 - < 18
 - 3) 18 - < 65
 - 4) 65+
- d. Number of prescriptions dispensed for FRPs and FNRP.

2. Reproductive Potential Status Changes (for each reporting period and cumulatively)

Both in a flowchart and in the report narrative, report the following regarding the *Change in Reproductive Potential Status and Prepubertal Annual Verification Forms* including:

- a. Number of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms* received, including the number of forms noted as a misclassification, error in classification, or correction to classification.
- b. Number of status changes to an FRP status, including the rationale for the change as indicated on the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*. Also, report:
 - i. Time between receipt of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)
 - ii. Verification that routine monthly pregnancy tests of all FRPs occurred prior to the next dispense following a change in status to an FRP
 - iii. Number of times Ambrisentan was dispensed prior to the patient getting their first pregnancy test following the status change to FRP, any resulting adverse events, and corrective actions
- c. Number of status changes to an FNRP, including rationale for the change as indicated on the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*
- d. The number of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms* returned reporting annual verification that a patient remains a Pre-Pubertal Female
- e. The number of *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms* returned reporting annual verification that a patient remains a Pre-Pubertal Female that are expected
- f. Number of shipments suspended as a result of the prescriber's failure to return the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* for pre-pubertal females
- g. Number of instances where a prescriber did not report a change or misclassification in the reproductive status of any female patient within 10 business days after the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* is signed.

- iv. Weeks gestation at termination if pregnancy terminated
 - v. Outcome for each pregnancy
 - vi. Age of patient
- b. Follow-up of outstanding pregnancy reports from the previous assessment reporting period
- c. Root cause analysis of each reported pregnancy to determine the reason the REMS program failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis
- 6. Evaluation of Knowledge of the Ambrisentan REMS Program and Risks of Ambrisentan Surveys (starting with the 12-month assessment then annually)**
- a. An evaluation of certified prescribers' knowledge of:
 - i. the risks of embryo-fetal toxicity associated with ambrisentan
 - ii. the need to monitor patients at baseline and monthly
 - iii. the need to counsel patients about: these risks; the need to use highly reliable contraception; and the need for monthly monitoring
 - iv. the need to enroll patients in the REMS
 - b. An evaluation of certified inpatient, outpatient and specialty pharmacy authorized representatives' and trained pharmacists' knowledge of:
 - i. the risks of embryo-fetal toxicity
 - ii. the need to confirm that appropriate patient monitoring and counseling occur before dispensing Ambrisentan.
 - c. An evaluation of enrolled patients' knowledge of:
 - i. the risks of embryo-fetal toxicity
 - ii. appropriate baseline and monthly monitoring
 - iii. appropriate contraception.
7. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its

- goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
 - f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications,* provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022081 REMS ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission 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

or

**NEW SUPPLEMENT FOR NDA 022081/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 022081/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 022081/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022081/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 022081

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
301 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
03/28/2019 03:26:30 PM

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Letairis (ambrisentan) tablets, for oral use
Initial U.S. Approval: 2007

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- Do not administer Letairis to a pregnant female because it may cause fetal harm (4.1, 5.1, 8.1).
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception (2.2, 8.3).
- For all female patients, Letairis is available only through a restricted program called the Letairis Risk Evaluation and Mitigation Strategy (REMS) (5.2).

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.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%) (1).

DOSAGE AND ADMINISTRATION

- Initiate treatment at 5 mg once daily (2.1).
- May be started with tadalafil (2.1).
- Titrate at 4-week intervals as needed and tolerated (2.1).
- Do not split, crush, or chew tablets (2.1).

DOSAGE FORMS AND STRENGTHS

Tablet: 5 mg and 10 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1)
- Idiopathic Pulmonary Fibrosis (4.2)

WARNINGS AND PRECAUTIONS

- Fluid retention may require intervention (5.3).
- If patients develop acute pulmonary edema during initiation of therapy with Letairis, consider underlying pulmonary veno-occlusive disease and discontinue treatment if necessary (5.4).
- Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (5.5).
- Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.6).

ADVERSE REACTIONS

- Most common adverse reactions (>3% compared to placebo) are peripheral edema, nasal congestion, sinusitis, and flushing (6.1).
- When used in combination with tadalafil, most common adverse reactions (>5% compared with either monotherapy) are peripheral edema, headache, nasal congestion, cough, anemia, dyspepsia, and bronchitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at (1-800-445-3235, Option 3) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Cyclosporine increases ambrisentan exposure; limit ambrisentan dose to 5 mg once daily (7).

USE IN SPECIFIC POPULATIONS

- Breastfeeding: Choose Letairis or breastfeeding (8.2).
- Not recommended in patients with moderate or severe hepatic impairment (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2018

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals [see *Contraindications (4.1)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1)*].

Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.3)*].

Because of the risk of embryo-fetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS program [see *Warnings and Precautions (5.2)*].

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.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability [see *Clinical Studies (14.2)*].

Studies establishing effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

Initiate treatment at 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either the dose of Letairis or tadalafil can be increased, as needed and tolerated, to Letairis 10 mg or tadalafil 40 mg.

Do not split, crush, or chew tablets.

2.2 Pregnancy Testing in Females of Reproductive Potential

Initiate treatment with Letairis in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment [see *Use in Specific Populations (8.3)*].

3 DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg film-coated tablets for oral administration

- Each 5 mg tablet is square convex, pale pink, with “5” on one side and “GSI” on the other side.
- Each 10 mg tablet is oval convex, deep pink, with “10” on one side and “GSI” on the other side.

4 CONTRAINDICATIONS

4.1 Pregnancy

Letairis may cause fetal harm when administered to a pregnant female. Letairis is contraindicated in females who are pregnant. Letairis was consistently shown to have teratogenic effects when administered to animals. 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 [see *Warnings and Precautions (5.1, 5.2) and Use in Specific Populations (8.1)*].

4.2 Idiopathic Pulmonary Fibrosis

Letairis is contraindicated in patients with Idiopathic Pulmonary Fibrosis (IPF), including IPF patients with pulmonary hypertension (WHO Group 3) [see *Clinical Studies (14.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-fetal Toxicity

Letairis may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests [see *Dosage and Administration (2.2), and Use in Specific Populations (8.1, 8.3)*].

Letairis is only available for females through a restricted program under a REMS [see *Warnings and Precautions (5.2)*].

5.2 Letairis REMS Program

For all females, Letairis is available only through a restricted program called the Letairis REMS, because of the risk of embryo-fetal toxicity [see *Contraindications (4.1), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)*].

Notable requirements of the Letairis REMS program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the Letairis REMS program prior to initiating Letairis. Male patients are not enrolled in the REMS.
 - Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (8.3)*].
- Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis.

Further information is available at www.letairisrems.com or 1-866-664-5327.

5.3 Fluid Retention

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Letairis compared to placebo [see *Adverse Reactions (6.1)*]. Most edema was mild to moderate in severity.

In addition, there have been postmarketing 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.

Peripheral edema/fluid retention is more common with Letairis plus tadalafil than with Letairis or tadalafil alone.

5.4 Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as Letairis, the possibility of PVOD should be considered, and if confirmed Letairis should be discontinued.

5.5 Decreased Sperm Counts

Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with ambrisentan. Letairis may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility [see *Use in Specific Populations* (8.6) and *Nonclinical Toxicology* (13.1)].

5.6 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.

In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment.

There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion.

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.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see Warnings and Precautions (5.1), Use in Specific Populations (8.1)]
- Fluid Retention [see Warnings and Precautions (5.3)]
- Pulmonary Edema with PVOD [see Warnings and Precautions (5.4)]
- Decreased Sperm Count [see Warnings and Precautions (5.5)]
- Hematologic Changes [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

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 are presented from two 12-week, placebo-controlled studies (ARIES-1 and ARIES-2) in patients with pulmonary arterial hypertension (PAH), and one randomized, double-blind, active-controlled trial in 605 patients with PAH (AMBITION) comparing Letairis plus tadalafil to Letairis or tadalafil alone. The exposure to Letairis in these studies ranged from 1 day to 4 years (N=357 for at least 6 months and N=279 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 reactions that occurred in >3% more patients receiving Letairis than receiving placebo are shown in Table 1.

Table 1 Adverse Reactions with Placebo-Adjusted Rates >3% in ARIES-1 and ARIES-2

| Adverse Reaction | Placebo (N=132) | Letairis (N=261) | |
|------------------|--------------------|---------------------|----------------------|
| | 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 |

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

Few notable differences in the incidence of adverse 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 (≥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 PAH during the clinical trials in patients with PAH 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 PAH during the clinical trials in patients with PAH 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.

Combination Use with Tadalafil

The mean exposure to Letairis + tadalafil in the AMBITION study was 78.7 weeks. The adverse reactions that occurred in >5% more patients receiving Letairis + tadalafil than receiving Letairis or tadalafil monotherapy in AMBITION are shown in Table 2.

Table 2 Adverse Reactions Reported More Commonly (>5%) on Letairis + Tadalafil than on Letairis or Tadalafil Monotherapy (ITT) in AMBITION

| Adverse Reactions | Letairis + Tadalafil Combination Therapy (N=302) n (%) | Letairis Monotherapy (N=152) n (%) | Tadalafil Monotherapy (N=151) n (%) |
|--------------------------|---|---|--|
| Peripheral edema | 135 (45%) | 58 (38%) | 43 (28%) |
| Headache | 125 (41%) | 51 (34%) | 53 (35%) |
| Nasal congestion | 58 (19%) | 25 (16%) | 17 (11%) |
| Cough | 53 (18%) | 20 (13%) | 24 (16%) |
| Anemia | 44 (15%) | 11 (7%) | 17 (11%) |
| Dyspepsia | 32 (11%) | 5 (3%) | 18 (12%) |
| Bronchitis | 31 (10%) | 6 (4%) | 13 (9%) |

Peripheral edema was more frequent on combination therapy; however, there was no notable difference observed in the incidence of peripheral edema in elderly patients (≥65 years) versus younger patients (<65 years) on combination therapy (44% vs. 45%) or Letairis monotherapy (37% vs. 39%) in AMBITION.

Treatment discontinuations due to adverse events while on randomized treatment were similar across treatment groups: 16% for Letairis + tadalafil, 14% for Letairis alone, and 13% for tadalafil alone.

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 post-approval use of Letairis. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: anemia requiring transfusion [see *Warnings and Precautions (5.6)*] heart failure (associated with fluid retention), symptomatic hypotension, and hypersensitivity (e.g., angioedema, rash).

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)*].

7 DRUG INTERACTIONS

Multiple dose coadministration 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 coadministered with cyclosporine [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, Letairis may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. There are limited data on Letairis use in pregnant women. In animal reproduction studies, Letairis was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day [see *Animal Data*]. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications (4.1)*, *Warnings and Precautions (5.1)*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Letairis was teratogenic at oral dosages of ≥ 15 mg/kg/day (AUC 51.7 h $\cdot\mu$ g/mL) in rats and ≥ 7 mg/kg/day (24.7 h $\cdot\mu$ g/mL) in rabbits; it was not studied at lower dosages. These dosages are of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day (14.8 h $\cdot\mu$ g/mL) based on AUC. 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.

A preclinical study in rats has shown decreased survival of newborn pups (mid and high dosages) and effects on testicle size and fertility of pups (high dosage) following maternal treatment with ambrisentan from late gestation through weaning. The mid and high dosages were 51 x, and 170 x (on a mg/m² body surface area basis) the maximum oral human dose of 10 mg and an average adult body weight of 70 kg. These effects were absent at a maternal dosage 17 x the human dose based on mg/m².

8.2 Lactation

Risk Summary

It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in breastfed infants from Letairis, a decision should be made whether to discontinue breastfeeding or discontinue Letairis, taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and pregnancy test 1 month after stopping treatment with Letairis. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patient on the potential risk to the fetus and patient options [see *Boxed Warning and Dosage and Administration (2.2)*].

Contraception

Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception (intrauterine device [IUD], contraceptive implant, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Infertility

Males

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. Counsel patients about the potential effects on fertility [see *Warnings and Precautions (5.5)*].

8.4 Pediatric Use

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

Juvenile Animal Data

In juvenile rats administered ambrisentan orally once daily during postnatal day 7 to 26, 36, or 62, a decrease in brain weight (–3% to –8%) with no morphologic or neurobehavioral changes occurred after breathing sounds, apnea, and hypoxia were observed, at exposures approximately 1.8 to 7.0 times human pediatric exposures at 10 mg, based on AUC.

8.5 Geriatric Use

In the two placebo-controlled clinical studies of Letairis, 21% of patients were ≥ 65 years old and 5% were ≥ 75 years old. The elderly (age ≥ 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

Pre-existing 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 might 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.

Elevation of Liver Transaminases

Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure [see *Adverse Reactions (6.1, 6.2)*]. In patients who develop hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if elevations of liver aminotransferases are >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

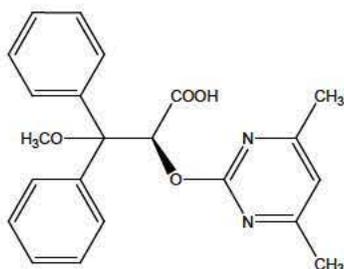
10 OVERDOSAGE

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 C₂₂H₂₂N₂O₄ 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:

Figure 1 Ambrisentan Structural Formula



Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pK_a 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 ($K_i=0.011$ nM) ET_A receptor antagonist with a high selectivity for the ET_A versus ET_B receptor (>4000-fold). The clinical impact of high selectivity for ET_A 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.

N-terminal pro-B-type natriuretic peptide (NT-proBNP)

In AMBITION [see *Clinical Studies (14.2)*], the decrease in NT-proBNP in patients on Letairis plus tadalafil was observed early (Week 4) and was sustained, with a reduction of 63% on Letairis plus tadalafil, 50% on Letairis alone, and 41% on tadalafil alone at Week 24.

12.3 Pharmacokinetics

The pharmacokinetics of ambrisentan (S-ambrisentan) in healthy subjects is 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

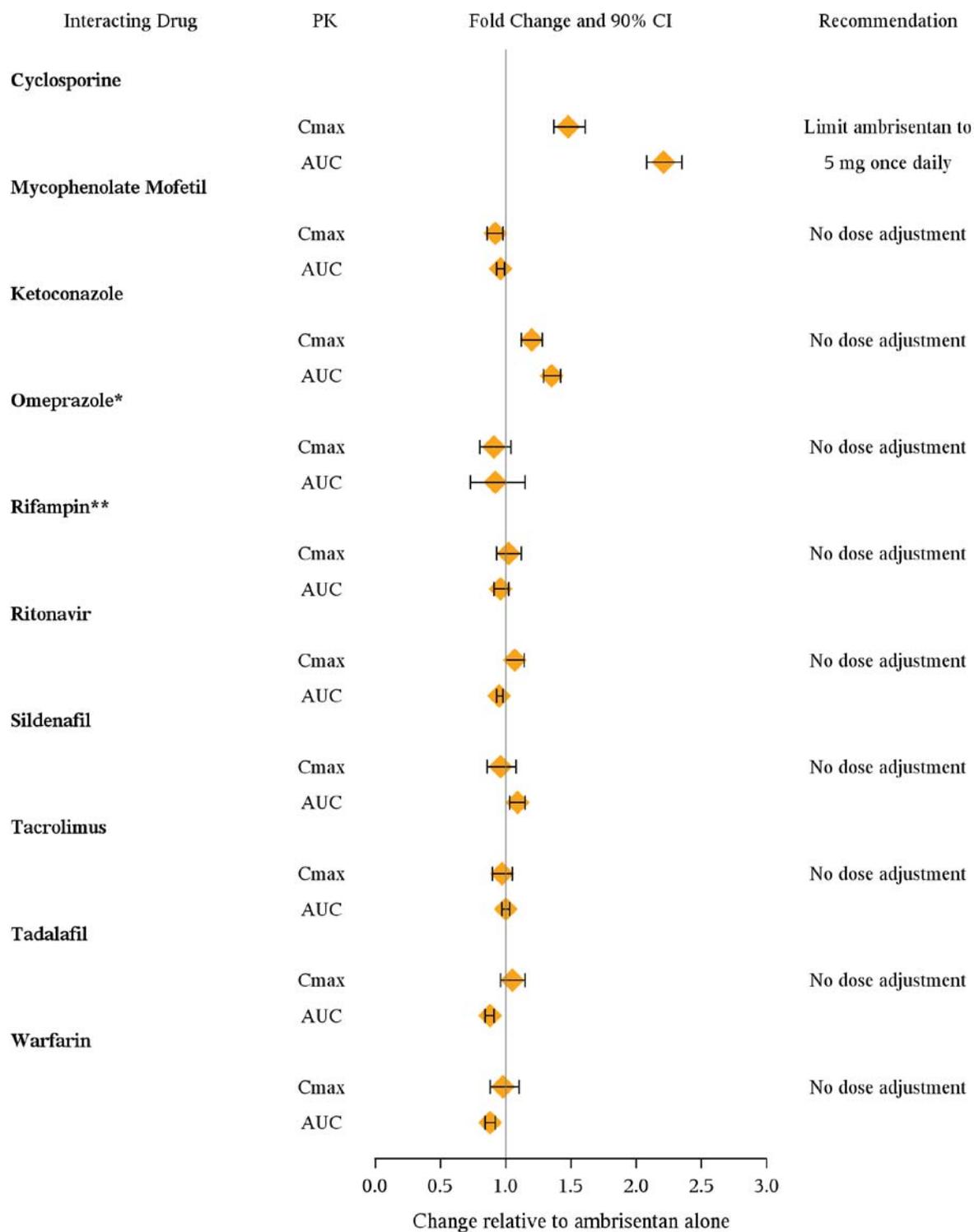
In Vitro Studies

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 Transporting Polypeptides OATP1B1 and OATP1B3, and 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)*]. In vitro studies found ambrisentan to have little to no inhibition of human hepatic transporters. Ambrisentan demonstrated weak dose-dependent inhibition of OATP1B1, OATP1B3, and NTCP (IC₅₀ of 47 μM, 45 μM, and approximately 100 μM, respectively) and no transporter-specific inhibition of BSEP, BRCP, P-gp, or MRP2. Ambrisentan does not inhibit or induce drug metabolizing enzymes at clinically relevant concentrations.

In Vivo Studies

The effects of other drugs on ambrisentan pharmacokinetics and the effects of ambrisentan on the exposure to other drugs are shown in Figure 2 and Figure 3, respectively.

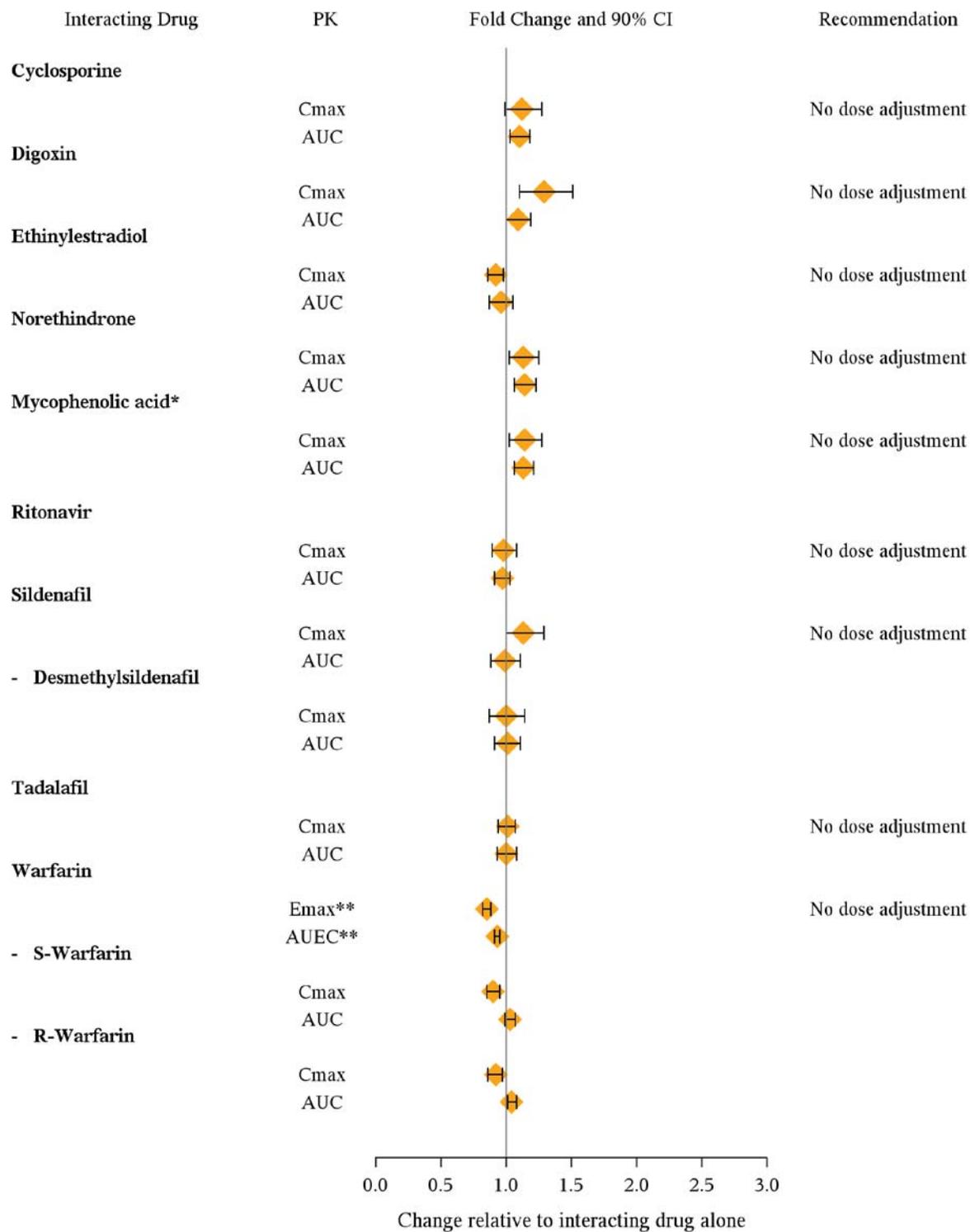
Figure 2 Effects of Other Drugs on Ambrisentan Pharmacokinetics



* Omeprazole: based on population pharmacokinetic analysis in PAH patients

** Rifampin: AUC and C_{max} were measured at steady-state. On Day 3 of coadministration a transient 2-fold increase in AUC was noted that was no longer evident by Day 7. Day 7 results are presented.

Figure 3 Effects of Ambrisentan on Other Drugs



* Active metabolite of mycophenolate mofetil

** GMR (95% CI) for INR

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/m² 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 ≥ 10 mg/kg/day (8-fold MRHD). Increased incidences of testicular findings were also observed in mice treated for two years at doses ≥ 50 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 ≥ 10 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 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[®] 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 3 and Figure 4.

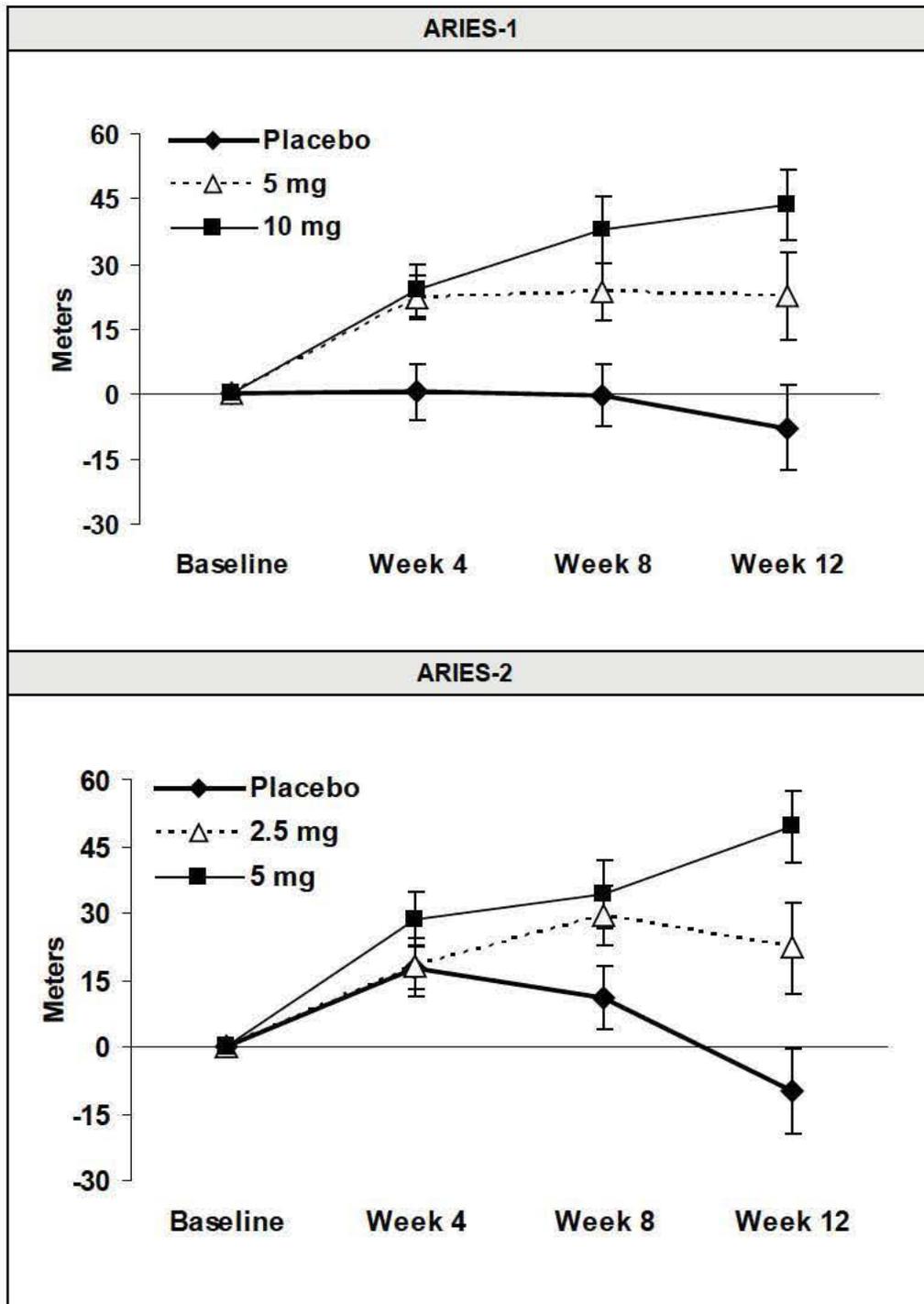
Table 3 Changes from Baseline in 6-Minute Walk Distance (meters) (ARIES-1 and ARIES-2)

| | 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 ^a | – | 0.008 | <0.001 | – | 0.022 | <0.001 |

Mean ± standard deviation

^a 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 4 Mean Change in 6-Minute Walk Distance (ARIES-1 and ARIES-2)



Mean change from baseline in 6-minute walk distance in the placebo and Letairis groups. Values are expressed as mean \pm 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 ≥ 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.

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 4 and Figure 5.

Table 4 Time to Clinical Worsening (ARIES-1 and ARIES-2)

| | ARIES-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, Log-rank test | – | 0.030 | – | 0.005 |

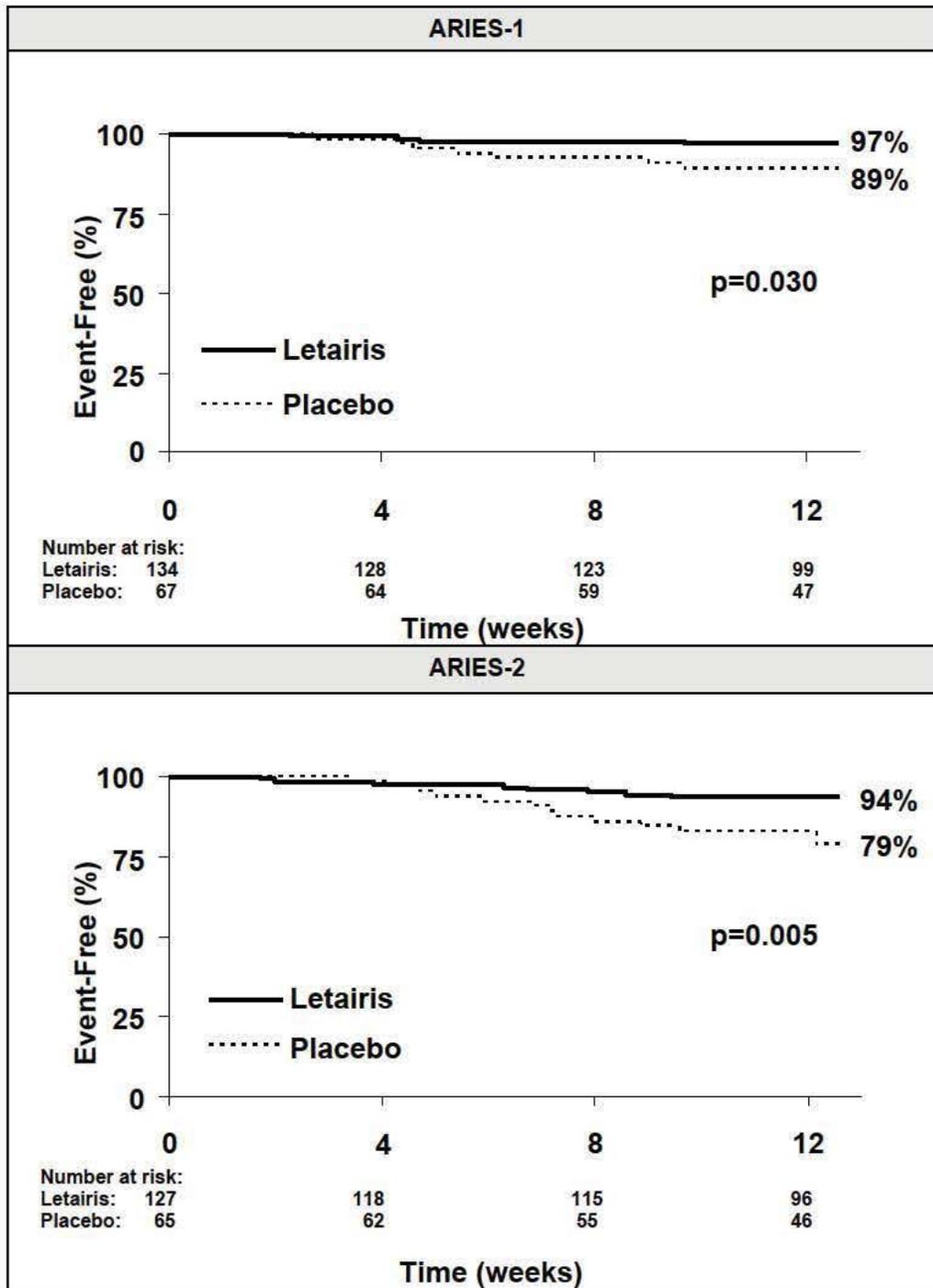
Intention-to-treat population.

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 5 Time to Clinical Worsening (ARIES-1 and ARIES-2)



Time from randomization to clinical worsening with Kaplan-Meier estimates of the proportions of patients without events 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.

14.2 Combination Treatment of PAH

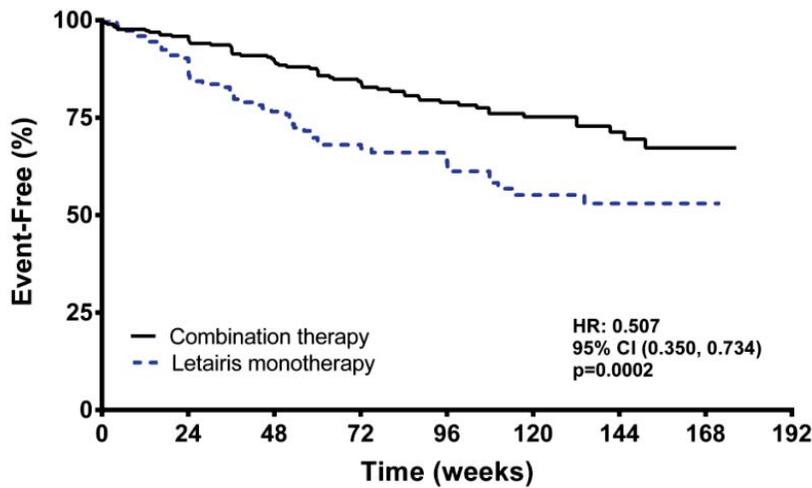
In a randomized, double-blind, active-controlled trial (AMBITION), 605 patients with WHO Functional Class II or III PAH were randomized 2:1:1 to once daily Letairis plus tadalafil or to Letairis or tadalafil alone. Treatment was initiated with Letairis 5 mg and tadalafil 20 mg. If tolerated, tadalafil was increased to 40 mg at 4 weeks and Letairis was increased to 10 mg at 8 weeks.

The primary endpoint was time to first occurrence of (a) death, (b) hospitalization for worsening PAH, (c) >15% decrease from baseline in 6MWD combined with WHO Functional Class III or IV symptoms sustained over 14 days (short term clinical worsening), or (d) reduction in 6MWD sustained over 14 days combined with WHO Functional Class III or IV symptoms sustained over 6 months (inadequate long term clinical response).

Patients had idiopathic PAH (55%), heritable PAH (3%), or PAH associated with connective tissue diseases, congenital heart disease, stable HIV infection, or drugs or toxins (APAH, 43%). Median time from diagnosis to first study drug administration was 25 days. Approximately 32% and 68% of patients were in WHO Functional Class II and III, respectively. The mean patient age was 55.7 years (34% were ≥65 years old). Most patients were white (90%) and female (76%); 45% were North American.

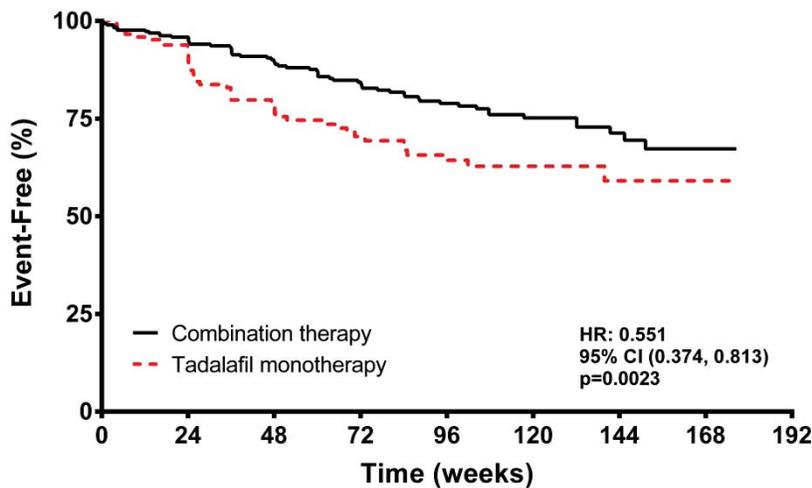
Principal results are shown in Figures 6 and 7.

Figure 6 Time to Primary Endpoint Event (AMBITION)



Number at risk:

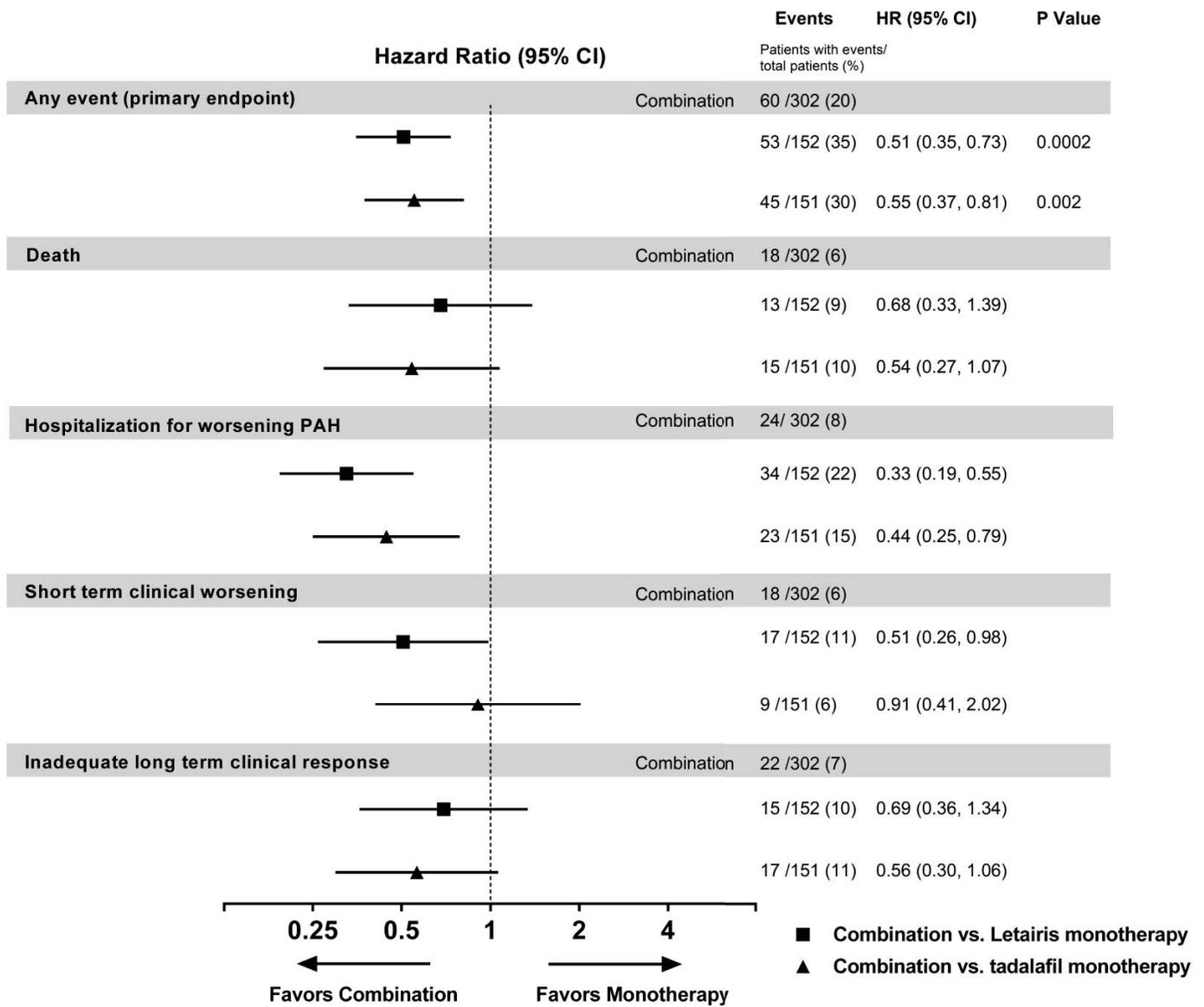
| | | | | | | | | |
|-----------------------|-----|-----|-----|-----|-----|----|----|---|
| Combination: | 302 | 270 | 217 | 170 | 126 | 85 | 45 | 9 |
| Letairis monotherapy: | 152 | 123 | 96 | 71 | 53 | 30 | 17 | 3 |



Number at risk:

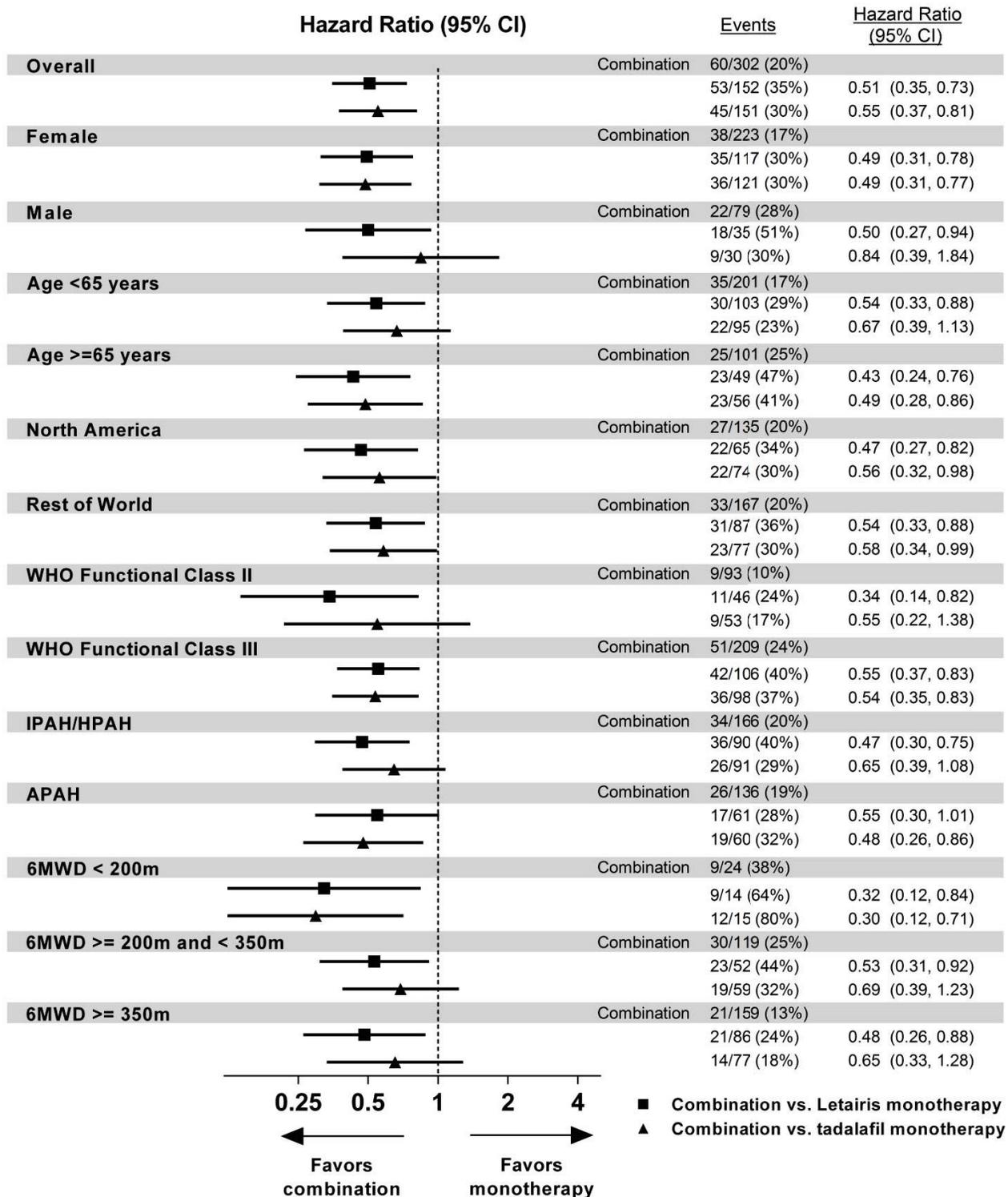
| | | | | | | | | |
|------------------------|-----|-----|-----|-----|-----|----|----|---|
| Combination: | 302 | 270 | 217 | 170 | 126 | 85 | 45 | 9 |
| Tadalafil monotherapy: | 151 | 128 | 92 | 65 | 48 | 33 | 15 | 3 |

Figure 7 Primary Endpoint Events and First Occurrences of Each Component at Any Time (AMBITION)



The treatment effect of Letairis plus tadalafil compared with individual monotherapy on time to first primary endpoint event was consistent across subgroups. (Figure 8).

Figure 8 Primary Endpoint by Subgroups (AMBITION)



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over interpreted.

Exercise Ability

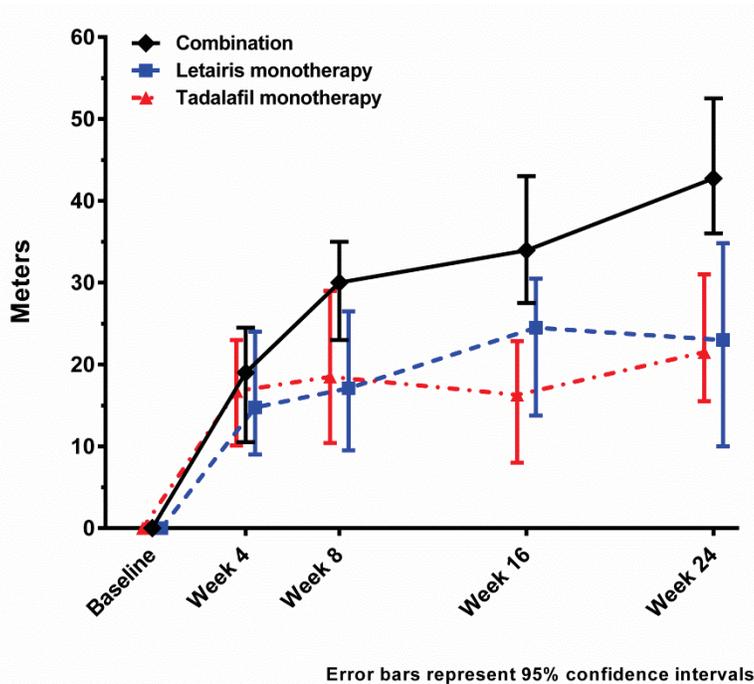
Results of the 6MWD at 24 weeks for the AMBITION study are shown in Table 5 and Figure 9.

Table 5 6-Minute Walk Distance at Week 24 (meters)^a (AMBITION)

| | Letairis + Tadalafil (N=302) | Letairis Monotherapy (N=152) | Tadalafil Monotherapy (N=151) |
|--|------------------------------|------------------------------|-------------------------------|
| Baseline (median) | 356 | 366 | 352 |
| Change from baseline (median) | 43 | 23 | 22 |
| Median difference from Letairis + Tadalafil (95% CI) | | 24 (11, 37) | 20 (8, 32) |
| P-Value | | 0.0004 | 0.0016 |

^a Missing values at Week 24 were imputed using Worst Rank scores for patients with an adjudicated clinical failure event of death or hospitalization, and Last Observed Carried Forward otherwise.

Figure 9 Median Change in 6-Minute Walk Distance (meters) in AMBITION



14.3 Long-term Treatment of PAH

In long-term follow-up of patients who were treated with Letairis (2.5 mg, 5 mg, or 10 mg once daily) in the two pivotal studies and their open-label extension (N=383), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 93%, 85%, and 79%, respectively. Of the patients who remained on Letairis for up to 3 years, the majority received no other treatment for PAH. 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 on mortality.

14.4 Adverse Effects in Idiopathic Pulmonary Fibrosis (IPF)

A randomized controlled study in patients with IPF, with or without pulmonary hypertension (WHO Group 3), compared Letairis (N=329) to placebo (N=163). The study was terminated after 34 weeks for lack of efficacy, and was found to demonstrate a greater risk of disease progression or death on Letairis. More patients taking Letairis died (8% vs. 4%), had a respiratory hospitalization (13% vs. 6%), and had a decrease in FVC/DLCO (17% vs. 12%) [see *Contraindications (4.2)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Letairis film-coated tablets are supplied as follows:

| Tablet Strength | Package Configuration | NDC No. | Description of Tablet; Debossed on Tablet; Size |
|-----------------|-----------------------|--------------|--|
| 5 mg | 30 count blister | 61958-0801-2 | Square convex; pale pink; "5" on side 1 and "GSI" on side 2; 6.6 mm Square |
| | 30 count bottle | 61958-0801-1 | |
| | 10 count blister | 61958-0801-3 | |
| | 10 count bottle | 61958-0801-5 | |
| 10 mg | 30 count blister | 61958-0802-2 | Oval convex; deep pink; "10" on side 1 and "GSI" on side 2; 9.8 mm x 4.9 mm Oval |
| | 30 count bottle | 61958-0802-1 | |
| | 10 count blister | 61958-0802-3 | |
| | 10 count bottle | 61958-0802-5 | |

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

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Embryo-fetal Toxicity

Instruct patients on the risk of fetal harm when Letairis is used in pregnancy [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*]. Female patients must enroll in the Letairis REMS program. Instruct females of reproductive potential to immediately contact their physician if they suspect they may be pregnant.

Letairis REMS Program

For female patients, Letairis is only available through a restricted program called the Letairis REMS [see *Contraindications (4.1), Warnings and Precautions (5.2)*]. Male patients are not enrolled in the Letairis REMS.

Inform female patients (and their guardians, if applicable) of the following notable requirements:

- All female patients must sign an enrollment form.
- Advise female patients of reproductive potential that they must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (8.3)*].

- Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure.
- Advise pre-pubertal females to report any changes in their reproductive status immediately to their prescriber.

Review the Letairis Medication Guide and REMS educational material with female patients.

A limited number of pharmacies are certified to dispense Letairis. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Hepatic Effects

Advise patients of the symptoms of potential liver injury and instruct them to report any of these symptoms to their physician.

Hematological Change

Advise patients of the importance of hemoglobin testing.

Other Risks Associated with Letairis

Instruct patients that the risks associated with Letairis also include the following:

- Decreases in sperm count
- Fluid overload

Administration

Advise patients not to split, crush, or chew tablets.

Gilead Sciences, Inc., Foster City, CA 94404

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GS22-081-016-PI

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
11/30/2018

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022081Orig1s039

REMS

RISK EVALUATION AND MITIGATION STRATEGY (REMS) Document

A. NDA 22-081 LETAIRIS¹® (ambrisentan) REMS Program

Initial REMS Approval: 05/2009

Most Recent Update: 03/2019

I. GOAL(S):

The goals of the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Letairis
2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Letairis
 - a. Females who are pregnant must not be prescribed Letairis
 - b. Females taking Letairis must not become pregnant

II. REMS ELEMENTS

A. Elements To Assure Safe Use

1. Healthcare providers who prescribe Letairis will be specially certified.
 - a. Gilead will ensure that physicians and other appropriately licensed healthcare professionals who prescribe Letairis are specially certified. Gilead will ensure that, to become certified, each prescriber agrees, on the *Prescriber Enrollment and Agreement Form*, that he or she has read the prescribing information (PI) and the *Prescriber Guide for the Letairis REMS Program*. The physician further agrees that he or she will:
 - i) Enroll all females in the Letairis REMS Program
 - ii) Determine whether each female is of reproductive potential as defined in the *Prescriber Guide for the Letairis REMS Program*
 - iii) Advise all females that Letairis is only available through a restricted distribution program called the Letairis REMS Program

¹ Letairis-specific requirements contained in this document apply until the date of full approval of the first abbreviated new drug application (ANDA) referencing Letairis.

iv) For FRP:

- (1) Educate FRPs about the risk of teratogenicity, the need to use highly reliable contraception as defined in the *Prescriber Guide for the Letairis REMS Program* during Letairis treatment and for one month following treatment discontinuation, and the need to use emergency contraception if required
- (2) Order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for one month after stopping Letairis treatment
- (3) Counsel a female patient if she is not complying with the required testing or if she is not using appropriate contraception as specified for FRP
- (4) Review with FRP the *Letairis REMS Program Guide for Female Patients* prior to initiating treatment
- (5) Report any changes in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

v) For Pre-Pubertal Females:

- (1) Educate Pre-Pubertal Female patient and parent/guardian about the risk of teratogenicity
- (2) Review the *Letairis REMS Program Guide for Female Patients* with the patient and parent/guardian
- (3) Regularly evaluate Pre-Pubertal Females for any change in reproductive status while receiving Letairis
- (4) Verify and document status as Pre-Pubertal Female at least annually for Pre-Pubertal Females who are at least 8 years of age and older by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- (5) Report any change in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

vi) For Post-Menopausal Females:

- (1) Report any misclassification in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware.
- (2) Report adverse events and any pregnancies during Letairis treatment to Gilead with all available information required for the Form FDA 3500A

vii) For Females with Other Medical Reasons for Permanent, Irreversible Infertility:

- (1) Report any misclassification in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware.

(2) Report adverse events and any pregnancies during Letairis treatment to Gilead with all available information required for the Form FDA 3500A

b. Gilead will:

- i) Ensure that prescribers' enrollment information and date of agreement are linked to their enrolled female patients' information in a validated database
- ii) For all females, ensure that the patient information from a new prescriber is linked in the Letairis REMS Program database with information from the prior prescriber
- iii) Ensure that the Letairis REMS Coordinating Center annually contacts the prescriber of a Pre-Pubertal Female to ensure that the prescriber verifies the Pre-Pubertal Female's reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- iv) Maintain a validated database of certified prescribers in the Letairis REMS Program. Gilead will ensure that prescribers' certification requirements are met and may de-enroll noncompliant prescribers until the requirements are met
- v) Ensure that within 60 days of REMS modification approval, all materials listed in or appended to the Letairis REMS will be available through the Letairis REMS Program website (www.letairisrems.com) or by calling the Letairis REMS Coordinating Center at 1-866-664-5327

c. The following materials are part of the Letairis REMS Program and are appended:

- i) *Prescriber Enrollment and Agreement Form*
- ii) *Prescriber Guide for the Letairis REMS Program*
- iii) *Letairis REMS Program Guide for Female Patients*
- iv) *Letairis REMS Patient Enrollment and Consent Form*
- v) *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- vi) *Letairis REMS website (www.letairisrems.com)*

2. Pharmacies, practitioners, and health care settings that dispense Letairis (dispensers) will be specially certified.

a. Gilead will ensure that pharmacies, practitioners, and health care settings that dispense Letairis are specially certified. Gilead will ensure that, to be certified, pharmacies, practitioners, and health care settings that dispense Letairis attest that:

- i) For all female patients, they will dispense Letairis only to patients enrolled in the Letairis REMS Program
- ii) Certified pharmacies will dispense Letairis to female patients only after receipt of *Letairis REMS Patient Enrollment and Consent Form* from the Letairis REMS Coordinating Center
- iii) Certified pharmacies will confirm any change in a female patient's reproductive potential status through the Letairis REMS Coordinating Center

iv) For FRP (as defined in the *Prescriber Guide for the Letairis REMS Program*):

- (1) Counsel FRP on the risk of serious birth defects and the need to use highly reliable contraception (as defined in the *Prescriber Guide for the Letairis REMS Program*) during Letairis treatment and for one month after stopping Letairis treatment
- (2) Inform FRP of the need to complete a monthly pregnancy test and to inform their prescriber immediately if they suspect they may be pregnant
- (3) Speak with each FRP, or their prescriber, every month before dispensing Letairis to obtain confirmation that pregnancy testing was completed
- (4) Dispense Letairis to FRP no more than a 30-day supply and only upon completing the following process:
 - (a.) Obtain confirmation from FRP that the pregnancy testing was completed
 - (b.) If unable to obtain confirmation from FRP that the pregnancy testing was completed, or if the FRP cannot be reached, the certified pharmacy will obtain confirmation from the patient's prescriber
 - (c.) If the prescriber for the FRP cannot confirm that the pregnancy testing was completed, the certified pharmacy will:
 - i. Remind the prescriber of his/her obligation to order and review monthly pregnancy tests
 - ii. Ask the prescriber whether or not he/she authorizes the refill of Letairis. The FRP is eligible to receive a 30-day supply of Letairis only if the prescriber authorizes the refill of Letairis

v) Notify Gilead of reports of adverse events and any reports of pregnancy and provide all available information needed for FDA Form 3500A

vi) Certified pharmacies will provide daily product dispensing data for FRP to the Letairis REMS Coordinating Center

b. Gilead will ensure the Letairis REMS Coordinating Center notifies certified pharmacies of patients' change in reproductive status within one business day of receipt of completed *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

c. Gilead will ensure that a designated representative of each certified pharmacy:

- i) Is trained on the requirements of the Letairis REMS Program
- ii) Trains dispensing staff on the Letairis REMS Program procedures and Letairis REMS materials as described above prior to dispensing Letairis to FRP
- iii) Agrees that the certified pharmacy may be audited by the FDA, Gilead, or a third party designated by Gilead

3. Letairis will be dispensed to FRP with evidence or other documentation of safe-use conditions:
 - a. Gilead will ensure that FRP treated with Letairis are enrolled in the Letairis REMS Program and assigned a unique patient identification number, before Letairis is dispensed by a certified pharmacy. Gilead will ensure that, to become enrolled, or when changing prescribers, each FRP must sign a *Letairis REMS Patient Enrollment and Consent Form* acknowledging that she has read the *Letairis REMS Program Guide for Female Patients*. By enrolling, the FRP agrees:
 - i) To be contacted, prior to each shipment of Letairis, to obtain confirmation that pregnancy testing was completed
 - ii) To be counseled on the requirements of the Letairis REMS Program and the risks of Letairis
 - iii) To be contacted by Gilead or the Letairis REMS Coordinating Center if she becomes pregnant while on Letairis or within 30 days after treatment discontinuation

B. Implementation System

The Implementation System will include the following:

1. Gilead will maintain a validated database of certified dispensers and females enrolled in the Letairis REMS Program to monitor and evaluate implementation of the elements provided for under Sections A.2 and A.3 above
2. Gilead will monitor the distribution of Letairis to ensure that the drug is only shipped to certified dispensers.
3. Gilead will track Letairis dispensing and review the location and amount of medication dispensed by certified pharmacies to FRPs.
4. Gilead will audit all certified pharmacies and the Letairis REMS Coordinating Center at the initiation of the Letairis REMS Program to ensure they implement the program as directed. Thereafter, Gilead will include the certified pharmacies and the Letairis REMS Coordinating Center in the company's annual audit plan
5. Gilead will monitor and evaluate the implementation of the elements provided for under Sections A.1, A.2, and A.3, above, in the manner described in the Letairis REMS Supporting Document, and take reasonable steps to work to improve implementation of these elements
6. Gilead will monitor the certified pharmacies to ensure their compliance with the Letairis REMS Program and will institute corrective actions if they are found non-compliant

C. Timetable for Submission of Assessments

Gilead will submit Letairis REMS assessments to the FDA annually no later than August 23rd. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 70 days before the submission date for that assessment. Gilead will submit each assessment so that it will be received by the FDA on or before the due date.

The requirements of the shared system REMS for ambrisentan apply as of the date of full approval of the first Abbreviated New Drug Application (ANDA) referencing Letairis

B. Ambrisentan Shared System REMS Program

I. Administrative Information

Initial Shared System REMS Approval: 03/2019

II. REMS Goal

The goal of the Ambrisentan REMS Program is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan by:

1. Ensuring prescribers are educated on the following:
 - o the risk of embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
 - o counseling patients about the risk and the need for monthly monitoring
 - o enrolling patients in the Ambrisentan REMS Program
 - o monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
 - o the risk of embryo-fetal toxicity
4. Ensuring that pharmacies are educated on and adhere to the following:
 - o confirming that the appropriate patient monitoring and counseling has occurred before dispensing ambrisentan
5. Ensuring that patients are informed about:
 - o the risk of embryo-fetal toxicity
 - o appropriate baseline and monthly patient monitoring
 - o appropriate contraception

III. REMS Requirements

Ambrisentan Applicants must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe ambrisentan must:

To become certified to prescribe

1. Review the drug's Prescribing Information.
 2. Review the following: [Prescriber and Pharmacy Guide](#).
 3. Enroll in the REMS by completing the [Prescriber Enrollment Form](#) and submitting it to the REMS Program.
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| Before treatment initiation (first dose) | <ol style="list-style-type: none"> 4. For all females: Assess the patient’s reproductive status using the definitions in the Prescriber and Pharmacy Guide. Document and submit the results to the REMS Program using the Patient Enrollment Form. 5. For all females: Counsel the patient that the drug is only available through a restricted distribution program. 6. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, and emergency contraception using the Guide for Female Patients. 7. For females of reproductive potential: Assess the patient’s pregnancy status by ordering and reviewing her pregnancy test result. 8. For pre-pubertal females: Counsel the patient on the risk of embryo-fetal toxicity using the Guide for Female Patients. 9. Enroll all female patients by completing the Patient Enrollment Form and submitting it to the REMS Program. |
| During treatment; before each prescription | <ol style="list-style-type: none"> 10. For females of reproductive potential: Counsel the patient if she is not complying with the required testing or if she is not using appropriate contraception. 11. For females of reproductive potential: Assess the patient’s pregnancy status by ordering and reviewing her pregnancy test result. |
| During treatment; at least annually | <ol style="list-style-type: none"> 12. For pre-pubertal females at least age 8 or older: Document reproductive status and submit to the REMS Program using Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form. |
| After treatment discontinuation; for one month | <ol style="list-style-type: none"> 13. For females of reproductive potential: Assess the patient’s pregnancy status by ordering and reviewing her pregnancy test result. |
| At all times | <ol style="list-style-type: none"> 14. For pre-pubertal females: Assess the patient’s reproductive status. 15. Report pregnancies to the REMS Program. |
| At all times, within 10 business days | <ol style="list-style-type: none"> 16. Report a change or misclassification in reproductive status to the REMS Program using the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form. |

2. Females of reproductive potential who are prescribed ambrisentan:

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| Before treatment initiation | <ol style="list-style-type: none">1. Review the Guide for Female Patients.2. Get a pregnancy test.3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program.4. Receive counseling from the prescriber on the risk of embryo-fetal toxicity and the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, and emergency contraception using the Guide for Female Patients. |
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| During treatment; before dispensing | <ol style="list-style-type: none">5. Receive counseling from the pharmacy or healthcare provider who dispenses ambrisentan on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, emergency contraception, to get monthly pregnancy tests, and to report a pregnancy immediately.6. Get a pregnancy test.7. Adhere to the safe use condition: Communicate with the pharmacy to confirm completion of pregnancy testing. |
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| During treatment and after treatment discontinuation for one month | <ol style="list-style-type: none">8. Adhere to the safe use condition: Use highly reliable contraception as described in the Guide for Female Patients. |
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| After treatment discontinuation; one month | <ol style="list-style-type: none">9. Get a pregnancy test. |
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3. Pre-pubertal females who are prescribed ambrisentan:

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| Before treatment initiation | <ol style="list-style-type: none">1. Review the Guide for Female Patients.2. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program.3. Receive counseling from the prescriber on the risk of embryo-fetal toxicity using the Guide for Female Patients. |
| At all times | <ol style="list-style-type: none">4. If over the age of 8: Be monitored for a change in reproductive status.5. Inform the prescriber if there is a change in your reproductive status. |
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4. Post-menopausal females or females with other medical reasons for permanent, irreversible infertility who are prescribed ambrisentan:

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| Before treatment initiation | <ol style="list-style-type: none">1. Review the Guide for Female Patients.2. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. |
| At all times | <ol style="list-style-type: none">3. Inform the prescriber if there is a change in your reproductive status. |

5. Outpatient pharmacies and healthcare providers that dispense ambrisentan must:

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| To become certified to dispense | <ol style="list-style-type: none">1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.2. Have the authorized representative review the Prescriber and Pharmacy Guide.3. Have the authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form and submitting it to the REMS Program.4. Train all relevant staff involved in dispensing ambrisentan on the REMS Program requirements using the Prescriber and Pharmacy Guide.5. Establish processes and procedures to verify the female patient is enrolled, the reproductive status of the patient has not changed, and the prescriber is certified.6. For females of reproductive potential: Establish processes and procedures to verify that pregnancy testing is complete or the prescriber authorizes the refill. |
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| Before dispensing | <ol style="list-style-type: none">7. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, emergency contraception, to get monthly pregnancy tests, and inform the prescriber of a pregnancy immediately.8. Verify the female patient is enrolled, the reproductive status has not changed, and the prescriber is certified through the processes and procedures established as a requirement of the REMS Program.9. For females of reproductive potential: Verify that the pregnancy testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS Program.10. For females of reproductive potential: Dispense no more than a 30 days' supply. |
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| At all times | <ol style="list-style-type: none">11. Report pregnancies to the REMS Program.12. Report a change or misclassification in reproductive status to the REMS Program.13. Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.14. For females of reproductive potential: Maintain and submit records of daily product dispensing data.15. Maintain records that all processes and procedures are in place and are being followed.16. Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed. |
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6. Inpatient pharmacies that dispense ambrisentan must:

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| To become certified to dispense | <ol style="list-style-type: none">1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.2. Have the authorized representative review the Prescriber and Pharmacy Guide.3. Have the authorized representative enroll in the REMS Program by completing Inpatient Pharmacy Enrollment Form and submitting it to the REMS Program.4. Train all relevant staff involved in dispensing ambrisentan on the REMS Program requirements using the Prescriber and Pharmacy Guide.5. Establish processes and procedures to verify the female patient is enrolled or will be enrolled in the REMS Program prior to discharge, her reproductive |
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status, and the female patient is under the supervision and care of a certified prescriber.

6. For females of reproductive potential: Establish processes and procedures to verify pregnancy testing is complete, the patient is counseled on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.

Before dispensing

7. Verify the female patient is under the supervision and care of a certified prescriber, her reproductive status, she is enrolled or will be enrolled in the REMS Program prior to discharge through the processes and procedures established as a requirement of the REMS Program.
8. For females of reproductive potential: Verify that pregnancy testing is complete, the patient is counseled on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately through the processes and procedures established as a requirement of the REMS Program.

At discharge

9. Dispense no more than a 15 days' supply.

At all times

10. Report pregnancies to the REMS Program.
11. Report a change or misclassification in reproductive status to the REMS Program.
12. Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
13. Maintain records that all processes and procedures are in place and are being followed.
14. Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

7. Wholesalers-distributors that distribute ambrisentan must:

To be able to distribute

1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies.
 2. Train all relevant staff involved in distribution on the REMS Program requirements.
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- At all times
1. Distribute only to certified pharmacies.
 2. Maintain records of drug distribution.
 3. Comply with audits carried out by the manufacturers, or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.
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Ambrisentan Applicants must provide training to healthcare providers who prescribe ambrisentan.

The training includes the following educational material: [Prescriber and Pharmacy Guide](#). The Training must be available online and hard copy format via mail or fax.

Ambrisentan Applicants must provide training to pharmacies that dispense ambrisentan.

The training includes the following educational material: [Prescriber and Pharmacy Guide](#). The Training must be available online and hard copy format via mail or fax.

To support REMS Program operations, Ambrisentan Applicants must:

1. Establish and maintain a REMS Program website, www.ambrisentanrems.us.com. The REMS Program website must include the capability to complete prescriber and inpatient pharmacy certification or enrollment online, the capability to enroll and manage patients online, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).
2. Make the REMS Program website fully operational and all REMS materials available through website and REMS coordinating center prior to the marketing of any ambrisentan product covered by this REMS that was approved under an ANDA.
3. Establish and maintain a REMS coordinating center for REMS participants at 1-888-417-3172.
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and certified in the REMS Program.
5. Ensure prescribers and inpatient pharmacies are able to complete the certification process by fax and online.
6. Ensure outpatient pharmacies are able to complete the certification process by fax.
7. Ensure prescribers are able to report change in reproductive status by fax and online.
8. Ensure prescribers are able to complete the patient enrollment process by fax and online.
9. Ensure pharmacies are able to confirm patient enrollment and prescriber certification before dispensing by phone and online.
10. Ensure that the REMS coordinating center contacts the prescriber of a pre-pubertal female annually to have the prescriber verify the pre-pubertal female's reproductive status by completing the [Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form](#).
11. Ensure the REMS coordinating center updates the database and notifies certified pharmacies of a patient's change in reproductive status within one business day of receipt of a completed [Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form](#).
12. Ensure pharmacies are able to enroll as inpatient (including, but not limited to, pharmacies in hospitals, long-term care facilities, prisons, and state psychiatric units) or outpatient pharmacies.
13. Notify prescribers and pharmacies within one business day after they become certified in the REMS Program.
14. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.

15. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.

To ensure REMS participants' compliance with the REMS Program, Ambrisentan Applicants must:

16. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: ambrisentan distribution and dispensing; certification of prescribers, pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
17. Establish a plan for addressing noncompliance with REMS Program requirements.
18. Monitor prescribers, pharmacies, and wholesaler-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
19. Audit all certified outpatient pharmacies, registered wholesalers-distributors and the REMS coordinating center within 180 calendar days of being certified/registered in the REMS and annually to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements, and include risk-based auditing of inpatient pharmacies annually.
20. Take reasonable steps to improve implementation of and compliance with the requirements in the REMS Program based on monitoring and evaluation of the REMS Program.

IV. REMS Assessment Timetable

Ambrisentan NDA Applicants must submit REMS Assessments annually from the date of the initial REMS approval (03/28/2019). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Ambrisentan NDA Applicants must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Ambrisentan REMS:

Enrollment Forms

Prescriber:

1. [Prescriber Enrollment and Agreement Form](#)

Patient:

2. [Patient Enrollment and Consent Form](#)

Pharmacy:

3. [Outpatient Pharmacy Enrollment Form](#)
4. [Inpatient Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

5. [Prescriber and Pharmacy Guide](#)

Patient:

6. [Guide for Female Patients](#)

Pharmacy:

7. [Prescriber and Pharmacy Guide](#)

Patient Care Form

8. [Change in Reproductive Status and Pre-Pubertal Annual Verification Form](#)

Other Materials

9. [REMS Program website \(www.ambrisentanrems.us.com\)](http://www.ambrisentanrems.us.com)

Letairis Risk Evaluation and Mitigation Strategy (REMS) Program

Prescriber Enrollment and Agreement Form

To be enrolled into the Letairis REMS Program, complete and submit this form.

Complete the form online at www.letairisrems.com or fax this form to 1-888-882-4035.

| 1 Prescriber Information | | | | |
|--|----------------------------|---------------------------------------|---------|--|
| First Name: | Middle Initial: | Last Name: | Suffix: | |
| Specialty: | Name of Facility: | Office Contact (First and Last Name): | | |
| Address: | City: | State: | ZIP: | |
| E-mail: | Phone: () | Fax: () | | |
| State License #: | NPI #: | | | |
| 2 Prescriber Agreement | | | | |
| <p>By signing below, you signify your understanding of the risks of Letairis® (ambrisentan) treatment and your obligation as a Letairis prescriber to educate your female patients about these risks, counsel them on risk reduction, monitor them appropriately, and report adverse events to the Letairis REMS Coordinating Center. Specifically, you attest to the following:</p> <ul style="list-style-type: none">• I have read the Prescribing Information and the <i>Prescriber Guide for the Letairis REMS Program</i> and agree to comply with the Letairis REMS Program requirements• I agree to enroll all female patients into the Letairis REMS Program• I will determine the reproductive potential status of all female patients using the definitions provided in the <i>Prescriber Guide for the Letairis REMS Program</i>• I will advise all female patients that Letairis is only available through a restricted distribution program called the Letairis REMS Program• I will counsel Females of Reproductive Potential on the risks of Letairis, including the risk of serious birth defects, and review the <i>Letairis REMS Program Guide for Female Patients</i> with the patient• I will counsel the Pre-Pubertal Female patient and parent/guardian on the risks of Letairis, including the risk of serious birth defects, and review the <i>Letairis REMS Program Guide for Female Patients</i> with the patient and parent/guardian• I will verify the reproductive potential status annually for Pre-Pubertal Females who are 8 years of age and older• I will order and review pregnancy tests for Females of Reproductive Potential prior to initiating treatment with Letairis, monthly during treatment, and for 1 month after stopping treatment• I agree to report any change in reproductive potential status by submitting a <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> within 10 business days of becoming aware of the change• I will counsel Females of Reproductive Potential to use highly reliable contraception during Letairis treatment, and for 1 month after stopping treatment, and the need to use emergency contraception if required• I will counsel female patients who fail to comply with the Letairis REMS Program requirements• I will notify the Letairis REMS Coordinating Center of any adverse events, or if any patient becomes pregnant during Letairis treatment or within 1 month after stopping treatment | | | | |
| REQUIRED | Prescriber Signature: X | Date: | | |

Please visit www.letairisrems.com or call 1-866-664-5327 for more information about the Letairis REMS Program.



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LETAIRIS RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Prescriber Guide for the Letairis REMS Program

Changes to the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program (XXXXXX)

- Revised: *Prescriber Guide for the Letairis REMS Program*: Risk of teratogenicity and removal of Medication Guide
- Revised title and content: *Letairis REMS Program Guide for Females Who Can Get Pregnant* to *Letairis REMS Program Guide for Female Patients*
- Removal of the Medication Guide from REMS materials
 - Revised form: *Letairis REMS Patient Enrollment and Consent Form*
 - Revised form: *Prescriber Enrollment and Agreement Form*
- Updated: REMS Website (www.letairisrems.com)

This guide is part of an FDA-approved REMS.
Reference ID: 4411238



Letairis[®]
ambrisentan

5 mg and 10 mg Tablets

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Letairis REMS Program

Overview of the Letairis REMS Program

- Letairis is only available to females through a restricted distribution program
- Prescribers must enroll in the Letairis REMS Program and comply with the Letairis REMS Program requirements to prescribe Letairis
- All female patients must enroll in the Letairis REMS Program to receive Letairis
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females on the risks of Letairis, including the risk of serious birth defects. The parent/guardian of the Pre-Pubertal Female must also be educated and counseled on the risks of Letairis
- Prescribers must order and review pregnancy tests for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment

Summary of the Letairis REMS Program Requirements by Patient Category

| Requirement | Female of Reproductive Potential | Female of Non-Reproductive Potential | | |
|---|----------------------------------|--------------------------------------|-----------------|---|
| | | Pre-Pubertal | Post-Menopausal | Other medical reasons for permanent, irreversible infertility |
| Prescriber enrolls female patients into Letairis REMS Program | × | × | × | × |
| Counseling with <i>Letairis REMS Program Guide for Female Patients</i> | × | × | | |
| Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment | × | | | |
| Prescriber must verify reproductive status annually by completing the <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> for females who are at least 8 years of age and older | | × | | |
| Prescriber must complete the <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> upon becoming aware of any change in reproductive potential status within 10 business days of awareness | × | × | × | × |

^{*}Counsel Pre-Pubertal Female patient and parent/guardian

Your Role in the Letairis REMS Program

Prescribers must complete the following steps in the Letairis REMS Program:

1. Read the Letairis Prescribing Information and this guide to understand the Letairis REMS Program and the risks of Letairis

2. Complete the Prescriber Enrollment and Agreement Form

- You will attest to understanding the risks of Letairis and agree to comply with the requirements of the Letairis REMS Program
- Complete the form online at www.letairisrems.com or fax the completed form to the Letairis REMS Coordinating Center at **1-888-882-4035**

3. Determine the reproductive potential status of female patients

Females of Reproductive Potential:

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined in the following column)

- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non-Reproductive Potential:

- **Pre-Pubertal Females:** Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- **Post-Menopausal Females:** Females who have passed through Menopause (as defined below)
- **Females with other medical reasons for permanent, irreversible infertility**

Definition of Menopause:

- Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy

4. Educate/counsel all female patients about risks of Letairis and about the Letairis REMS Program

- Advise all females that Letairis is only available through a restricted distribution program called the Letairis REMS Program



For females with other medical reasons for permanent, irreversible infertility:

- Report any misclassification in reproductive potential status by completing the *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* within 10 business days of becoming aware

5. Check pregnancy status (in Female of Reproductive Potential)

- Order and review pregnancy tests for the patient:
 - Prior to initiating treatment
 - Monthly during treatment
 - 1 month after stopping treatment

The patient must agree to be contacted by the Certified Pharmacy prior to each shipment to confirm that a pregnancy test was completed, and she must also agree to be contacted by the Letairis REMS Coordinating Center if she becomes pregnant while on Letairis or within 1 month of stopping treatment.

6. Enroll all female patients into the Letairis REMS Program

- Access, complete and submit the Letairis REMS patient enrollment online at www.letairisrems.com. Alternatively, complete a paper version of the *Letairis REMS Patient Enrollment and Consent Form* and fax the completed form, along with all patient insurance information, including prescription drug benefits and medical benefits, to the Letairis REMS Coordinating Center at **1-888-882-4035**
- Keep the original form with the patient's records

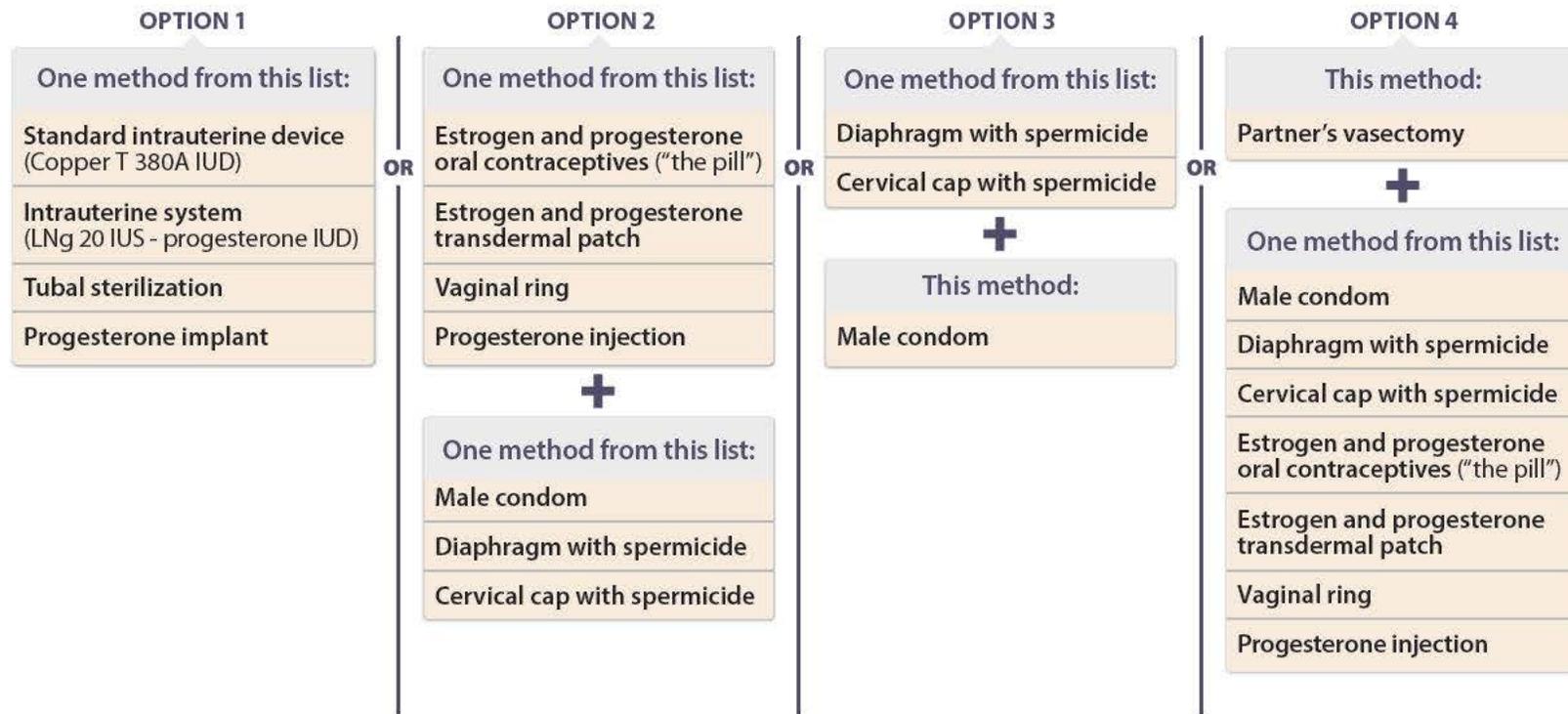
7. Evaluate reproductive potential status of female patients throughout treatment

- Report any change in patient's reproductive potential status within 10 business days of becoming aware of the change to the Letairis REMS Coordinating Center by faxing the completed *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* to **1-888-882-4035**



Contraceptive Options for Females of Reproductive Potential

Contraceptive Options for Females of Reproductive Potential





Role of Certified Pharmacies

The Letairis REMS Coordinating Center

For a list of Certified Pharmacies, call the Letairis REMS Coordinating Center at **1-866-664-5327**

Additional questions

Please visit www.letairisrems.com or call the Letairis REMS Coordinating Center at **1-866-664-5327** for more information about the Letairis REMS Program.

Please see the accompanying patient Medication Guide and Prescribing Information, including **BOXED WARNING**, for more complete information.



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Letairis
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LETAIRIS RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Letairis REMS Program Guide for Female Patients

This guide is part of an FDA-approved REMS.

Reference ID: 4411238



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Information for Female Patients

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Information for Female Patients

What is Letairis?

What is the Letairis Risk Evaluation and Mitigation Strategy (REMS) Program?

What are the serious risks of Letairis?



How do I enroll in the Letairis REMS Program?

What are the Letairis REMS Program requirements for me?

Females Who Can Get Pregnant:

You are considered to be a female who can get pregnant if you have entered puberty, have a uterus, and have not passed through Menopause.

To receive Letairis, you must:

- **Have a negative pregnancy test before you start taking Letairis and before you receive your refills. Your doctor orders the pregnancy tests for you. Your Certified Pharmacy will call you and ask if you have taken this test before shipping your refill**
- **Be sure you take your monthly pregnancy tests as ordered by your doctor. You may not receive your Letairis refill on time if you do not take your monthly pregnancy tests**

Do not have unprotected sex. Use appropriate birth control during your Letairis treatment and for 1 month after stopping your Letairis treatment because the medicine may still be in your body. Page 5 of this guide shows your birth control options.

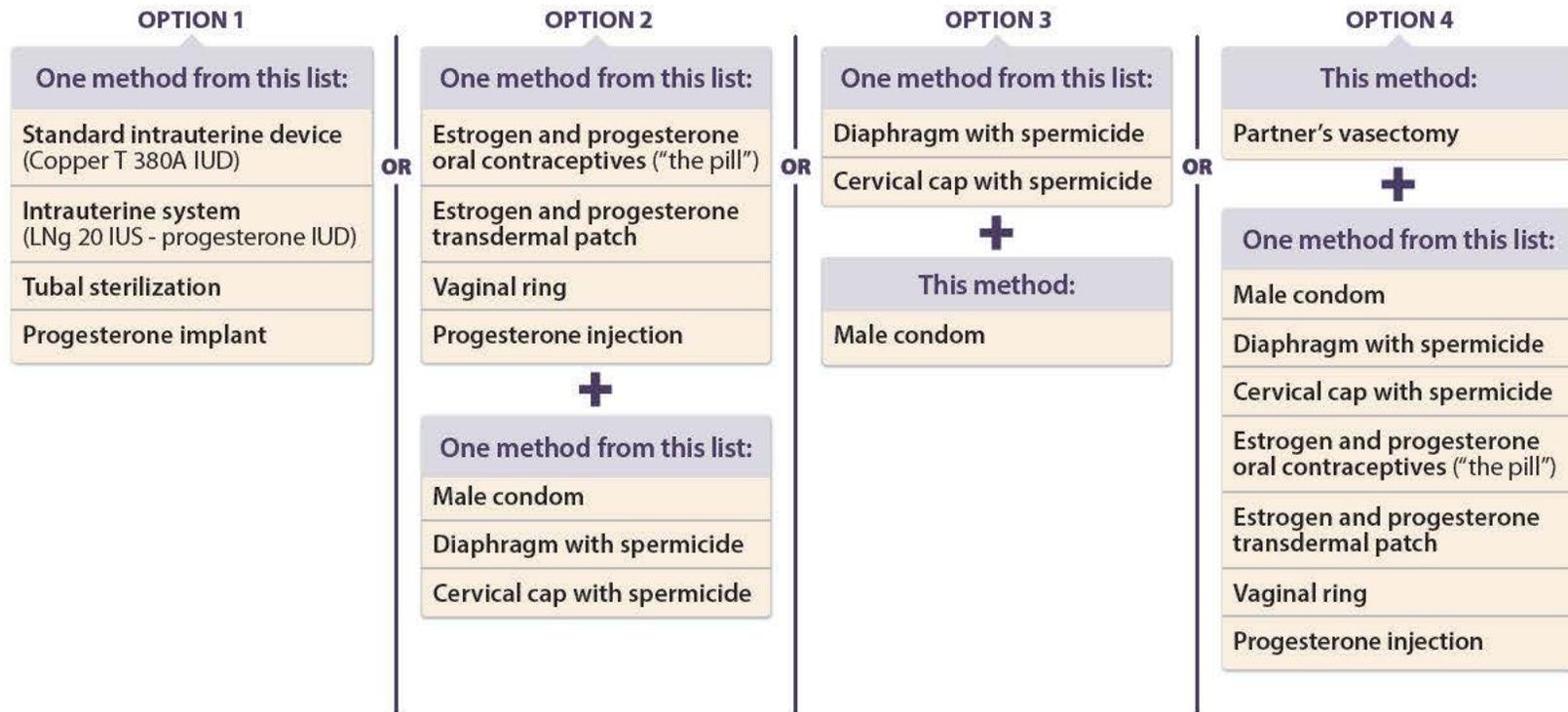
Talk to your doctor or pharmacist right away if you have unprotected sex, if you think your birth control has failed, or if you think you may be pregnant. Your doctor may tell you to use emergency birth control. Do not wait until your next appointment to tell your doctor if you miss your menstrual period or if you think you may be pregnant.

What are my birth control options?

If you are a female who can get pregnant, your doctor will talk to you about your birth control options. Use the diagram on the next page to help decide what birth control options are best for you. Talk to your doctor if you have questions about your birth control options. Tell your doctor if you want to change your birth control method.

You may choose from the four options listed on the next page. More than one birth control method might be needed every time you have sex (intercourse).

Your birth control options



How will I receive my Letairis?

Certified Pharmacies provide products and services for patients with certain diseases. Only Certified Pharmacies can provide Letairis to you. In some cases, your insurance company may require you to use a specific Certified Pharmacy.

Your Certified Pharmacy ships your Letairis refill to you. If you are a female who can get pregnant, before each shipment, you will be called to confirm that you have taken a monthly pregnancy test before refilling your prescription. **It is important that your Certified Pharmacy is able to contact you in order to avoid delays in your refills.**

If you have questions or concerns about Letairis, talk to your doctor. Please visit www.letairisrems.com or call **1-866-664-5327** for more information about the Letairis REMS Program.



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Reference ID: 4411238

Letairis REMS Patient Enrollment and Consent Form

Complete and submit the form online at www.letairisrems.com or fax this form to 1-888-882-4035.

1 Patient Information (PLEASE PRINT)

| | | | | | |
|-------------------------|--|---|-------------------------|----------------------|---------|
| First Name: | | Middle Initial: | Last Name: | | |
| Address: | | | City: | State: | Z P: |
| Birthdate: / / | Gender: <input type="checkbox"/> M <input type="checkbox"/> F | Preferred Time to Contact: <input type="checkbox"/> Day <input type="checkbox"/> Evening | Home Phone: () | Mobile Phone: () | E-mail: |
| Alternate Contact Name: | | | Alternate Phone: () | Relationship: | |

2 Female Patient Agreement

For All Females: I acknowledge that I have been counseled that Letairis is only available through a restricted distribution program under an FDA-required Risk Evaluation and Mitigation Strategy (REMS). I have read the *Letairis REMS Program Guide for Female Patients*. Permission to share personal and health information: I authorize my healthcare providers and pharmacies to share my personal and health information with Gilead Sciences, Inc., and its agents ("Gilead"), in order for Gilead to use and disclose my information to administer the Letairis REMS Program. Gilead agrees to protect my information and to use and share it only to administer the Letairis REMS program.

For Females Who Can Get Pregnant: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects. I have read the *Letairis REMS Program*

Guide for Female Patients. I understand that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risk of serious birth defects and the importance of not becoming pregnant, ensure that I have completed pregnancy testing before I start Letairis, monthly before each refill, and for 1 month after stopping Letairis, and obtain information about my pregnancy, if I become pregnant.

For Pre-Pubertal Females: I acknowledge that I have been counseled on the risks of Letairis, including the risk of serious birth defects, and that I have read the *Letairis REMS Program Guide for Female Patients*. Parent or guardian must sign below.

| | | |
|---|--|-------|
| REQUIRED FOR ALL FEMALE PATIENTS | Patient or Parent/Guardian Signature: X | Date: |
|---|--|-------|

3 Prescriber Information (PLEASE PRINT)

| | | | | | |
|---------------------------------------|--|-------------|------------------|---------|------|
| First Name: | | Last Name: | State License #: | | |
| Address: | | | City: | State: | Z P: |
| Phone: () | | Fax: () | | NPI #: | |
| Office Contact (First and Last Name): | | | | E-mail: | |

4 Statement of Medical Necessity

Diagnosis: Pulmonary Arterial Hypertension (The following list is not to suggest approved uses or indications. Please select one category below.)

- Primary Pulmonary Hypertension
 Pulmonary Hypertension, Secondary
 Pulmonary Heart Disease, Unspecified
 Other

5 Prescriber Authorization (REQUIRED FOR ALL FEMALE PATIENTS)

| | | |
|--|---|--|
| REQUIRED FOR ALL FEMALE PATIENTS | Only 1 box should be checked. For female patients, please indicate the patient's current reproductive status below. (Please see definitions of these terms below) | |
| | Female of Reproductive Potential Has a negative pregnancy test been confirmed prior to prescribing Letairis? <input type="checkbox"/> Yes <input type="checkbox"/> No | Female of Non-Reproductive Potential (choose one below) <input type="checkbox"/> Pre-Pubertal Female <input type="checkbox"/> Post-Menopausal Female <input type="checkbox"/> Other medical reasons for permanent, irreversible infertility |
| I certify that for female patients, I have provided the appropriate counseling and Letairis REMS materials, and I will continue to fulfill my obligations under the Letairis REMS Program. | | |
| REQUIRED FOR ALL PRESCRIBERS | Prescriber Signature: X | Date: |

Definitions:

Females of Reproductive Potential

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).
- For the purposes of REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

Females of Non-Reproductive Potential

- Pre Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post Menopausal Females: Females who have passed through Menopause (as defined below)
- Other medical reasons for permanent, irreversible infertility

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or postsurgical from bilateral oophorectomy.

Prescriber obligations under the Letairis REMS Program

For All Females

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Letairis is available only through a restricted distribution program under an FDA-required REMS.

- I will evaluate the patient and agree to document any change in reproductive potential status by submitting a *Change in Reproductive Potential Status and Pre Pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

For Females of Reproductive Potential

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis REMS Program Guide for Female Patients* with the patient (and parent/guardian when appropriate).
- I will order and review pregnancy tests prior to initiation of Letairis treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Letairis REMS Program.

For Pre-Pubertal Females

- I acknowledge that I have counseled the patient and parent/guardian on the risks of Letairis, including the risk of serious birth defects, and that I have reviewed the *Letairis REMS Program Guide for Female Patients* with the patient and parent/guardian.
- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older, and agree to report any change in reproductive potential status on a *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form* within 10 business days of becoming aware of the change.

6 Complete and submit the form online at www.letairisrems.com or fax this form to 1-888-882-4035.

Please visit www.letairisrems.com or call 1-866-664-5327 for more information about the Letairis REMS Program.

Please see accompanying patient Medication Guide and Prescribing Information, including **BOXED WARNING**.

This form is part of an FDA-approved REMS.



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Letairis Risk Evaluation and Mitigation Strategy (REMS) Program

Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form

FAX FORM TO: 1-888-882-4035

Complete this form to:

1. Change the reproductive status of any female patient, or
2. Complete the annual verification of reproductive potential status for Pre-Pubertal Females at least 8 years of age and older

Prescriber must complete this form within 10 business days of awareness of the change in reproductive potential status.

| 1 Patient Information (PLEASE PRINT) | | | |
|---|--|------------------|-------|
| Patient Letairis REMS ID: | | | |
| First Name: | Middle Initial: | Last Name: | |
| Address: | City: | State: | ZIP: |
| Birthdate: / / | Phone: () | | |
| 2 Prescriber Information (PLEASE PRINT) | | | |
| First Name: | Last Name: | State License #: | |
| Address: | City: | State: | ZIP: |
| Phone: () | Fax: () | NPI #: | |
| Office Contact (First and Last Name): | E-mail Address: | | |
| Definitions of Reproductive Potential Status: | | | |
| Females of Reproductive Potential | | | |
| <ul style="list-style-type: none">• Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).• For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal). | | | |
| Females of Non-Reproductive Potential | | | |
| <ul style="list-style-type: none">• Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.• Post-Menopausal Female: Females who have passed through Menopause (as defined below).• Other medical reasons for permanent, irreversible infertility. | | | |
| Menopause | | | |
| Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy. | | | |
| 3 Please select the most appropriate reason for submitting this form. | | | |
| Change in Status | | | |
| <ul style="list-style-type: none">• Based on definitions of reproductive potential status, patient is (please check one):<ul style="list-style-type: none"><input type="checkbox"/> Female of Reproductive Potential<input type="checkbox"/> Female of Non-Reproductive Potential – Patient is pre-pubertal<input type="checkbox"/> Female of Non-Reproductive Potential – Patient is post-menopausal<input type="checkbox"/> Female of Non-Reproductive Potential – Other medical reasons for permanent, irreversible infertility• Reason for change in classification (please check one):<ul style="list-style-type: none"><input type="checkbox"/> Physiological transition<input type="checkbox"/> Medical/surgical (please specify): _____<input type="checkbox"/> Other (please specify): _____ | | | |
| Annual Verification | | | |
| <input type="checkbox"/> Patient remains a Pre-Pubertal Female (8 years of age or older) | | | |
| REQUIRED | By signing, I certify that the patient's reproductive potential status and reason for submitting this form are accurately noted above. | | Date: |
| | Prescriber Signature: X | | |

Please visit www.letairisrems.com or call 1-866-664-5327 for more information about the Letairis REMS Program. This form is part of an FDA-approved REMS.



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For Female Patients



For Prescribers



The Letairis Risk Evaluation and Mitigation Strategy (REMS) Program

A Risk Evaluation and Mitigation Strategy is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

The purpose of the Letairis REMS Program is to:

- Inform prescribers, patients, and pharmacists about the risk of serious birth defects and safe-use conditions for Letairis
- Minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential prescribed Letairis
 - Females who are pregnant must not be prescribed Letairis
 - Females taking Letairis must not become pregnant

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Welcome to the Letairis Risk Evaluation and Mitigation Strategy Program

What is the Letairis REMS Program?

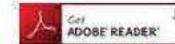
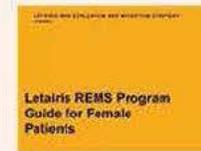
Because of the risk of serious birth defects, the FDA has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for Letairis. The purpose of the Letairis REMS Program is to make sure the benefits of Letairis outweigh the risks. All females must enroll in the Letairis REMS Program to receive Letairis; however, specific requirements apply to females who can get pregnant.

For Female Patients to receive Letairis:

- 1) You must talk with your doctor to ensure the benefits outweigh the risks of Letairis
- 2) You must agree to all of the requirements of the Letairis REMS Program. For women who can get pregnant, these requirements include monthly pregnancy tests and use of appropriate birth control while taking Letairis and for 1 month after stopping Letairis
- 3) Your doctor will enroll you in the Letairis REMS Program
- 4) Your prescription will be mailed to you from a Certified Pharmacy that you and your doctor will choose

For women who can get pregnant, learn more about the Letairis REMS Program.

Download this helpful guide.



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Overview of the
Letairis REMS Program

Changes to the
Letairis REMS Program

Overview of the Letairis REMS Program

- Prescribers must enroll in the Letairis REMS Program and comply with the Letairis REMS Program requirements to prescribe Letairis
- All female patients must enroll in the Letairis REMS Program to receive Letairis
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females as described in the *Prescriber Guide for the Letairis REMS Program*. The parent/guardian of the Pre-Pubertal Female must also be educated and counseled on the risks of Letairis
- Required pregnancy testing for Females of Reproductive Potential prior to writing a prescription for Letairis and monthly thereafter, including 1 month after stopping treatment with Letairis
- Letairis is only available through a restricted distribution program

Changes to the Letairis REMS Program (Month 2018)

- Revised: *Prescriber Guide for the Letairis REMS Program*: Risk of teratogenicity and removal of Medication Guide
- Revised title and content: *Letairis REMS Program Guide for Females Who Can Get Pregnant* to *Letairis REMS Program Guide for Female Patients*
- Removal of the Medication Guide from REMS materials
 - Revised form: *Letairis REMS Patient Enrollment and Consent Form*
 - Revised form: *Prescriber Enrollment and Agreement Form*
- Updated: REMS Website (www.letairisrems.com)

[back to top](#)

You can now enroll a female patient in the Letairis REMS Program online by [clicking here](#). Or, you can download the forms below and FAX, as directed.

Download Letairis REMS Materials

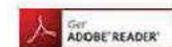
In order to ensure that Letairis is prescribed and taken safely, Gilead has worked with the FDA to develop materials for the Letairis REMS Program to inform prescribers and patients about the risk of serious birth defects.

Letairis REMS Program Prescriber Materials

-  **Prescriber Guide for the Letairis REMS Program**
-  **Prescriber Enrollment and Agreement Form**
-  **Letairis REMS Patient Enrollment and Consent Form**
-  **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**

Letairis REMS Program Patient Education Materials

-  **Letairis REMS Program Guide for Female Patients**



Overview of the
Letairis REMS Program

Changes to the
Letairis REMS Program

Overview of the Letairis REMS Program

- Prescribers must enroll in the Letairis REMS Program and comply with the Letairis REMS Program requirements to prescribe Letairis.
- All female patients must enroll in the Letairis REMS Program to receive Letairis.
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females as described in the *Prescriber Guide for the Letairis REMS Program*. The parent/guardian of the Pre-Pubertal

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You can now enroll a female patient in the Letairis REMS Program online by clicking [here](#). Or, you can download the forms below and FAX, as directed.

Download Letairis REMS Materials

In order to ensure that Letairis is prescribed and taken safely, Gilead has worked with the FDA to develop materials for the Letairis REMS program to inform prescribers and patients of the risk of serious birth defects.

Letairis REMS Program Prescriber Materials

- *Prescriber Guide for the Letairis REMS Program*
- *Prescriber Enrollment and Agreement Form*
- *Letairis REMS Patient Enrollment and Consent Form*
- *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*

Letairis REMS Program Patient Education Materials

- *Letairis REMS Program Guide for Female Patients*

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- Re
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- Me
- Revised title and content: *Letairis REMS Program Guide for Females Who Can Get Pregnant to Letairis REMS Program Guide for Female Patients*
- Removal of the Medication Guide from REMS materials
 - Revised form: *Letairis REMS Patient Enrollment and Consent Form*
 - Revised form: *Prescriber Enrollment and Agreement Form*
- Updated REMS Website (www.letairisrems.com)

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AMBRISENTAN RISK EVALUATION
AND MITIGATION STRATEGY (REMS)

Ambrisentan REMS
**PRESCRIBER AND
PHARMACY GUIDE**

This guide is part of an FDA-approved REMS.

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Ambrisentan REMS

Indication

Ambrisentan is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

Risk of embryo-fetal toxicity

Ambrisentan may cause fetal harm when administered to a pregnant female and is contraindicated during pregnancy. There is limited data on ambrisentan use in pregnant females; the possibility of serious birth defects in humans cannot be excluded.

Pregnancy must be excluded prior to the initiation of ambrisentan treatment, monthly thereafter, and for one month following treatment discontinuation.

Ambrisentan REMS

Because of the risk of serious birth defects, ambrisentan is only available to females through a restricted distribution program under an FDA-required REMS. The goal of the Ambrisentan REMS is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan by:

- Ensuring prescribers are educated on the following:
 - the risks of embryo-fetal toxicity
- Ensuring prescribers are educated on and adhere to the following:
 - counseling patients about these risks and the need for monthly monitoring
 - enrolling patients in the Ambrisentan REMS
 - monitoring patients at baseline and monthly
- Ensuring that pharmacies are educated on the following:
 - the risks of embryo-fetal toxicity
- Ensuring that pharmacies are educated on and adhere to the following:
 - confirming that the appropriate patient monitoring and counseling has occurred before dispensing ambrisentan
- Ensuring that patients are informed about:
 - the risks of embryo-fetal toxicity
 - appropriate baseline and monthly patient monitoring
 - appropriate contraception

Overview of the Ambrisentan REMS

- Ambrisentan is only available to females through a restricted distribution program
- Prescribers must enroll in the Ambrisentan REMS and comply with the Ambrisentan REMS requirements to prescribe ambrisentan
- All female patients must enroll in the Ambrisentan REMS to receive ambrisentan
- Prescribers must educate and counsel Females of Reproductive Potential and Pre-Pubertal Females on the risks of ambrisentan, including the risk of serious birth defects using the **Guide for Female Patients**. The parent/guardian of the Pre-Pubertal Female must also be educated and counseled on the risks of ambrisentan
- Prescribers must order and review pregnancy tests for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and for one month following treatment discontinuation

| Requirement | Female of Reproductive Potential | Female of Non-Reproductive Potential | | |
|--|----------------------------------|--------------------------------------|-----------------|---|
| | | Pre-Pubertal | Post-Menopausal | Other medical reasons for permanent, irreversible infertility |
| Prescriber enrolls female patients into Ambrisentan REMS | X | X | X | X |
| Review <i>Guide for Female Patients</i> | X | X | X | X |
| Counseling with <i>Guide for Female Patients</i> | X | X | | |
| Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for one month following treatment discontinuation | X | | | |
| Prescriber must verify reproductive status annually by completing the <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> for females who are at least 8 years of age and older | | X | | |
| Prescriber must complete the <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> upon becoming aware of any change in reproductive status within 10 business days of awareness | X | X | X | X |

Role of Prescriber in the Ambrisentan REMS

Prescribers must complete the following steps in the Ambrisentan REMS:

1. Read the Ambrisentan Prescribing Information and this guide to understand the Ambrisentan REMS and the risks of ambrisentan
2. Complete the *Prescriber Enrollment Form*
 - You will attest to understanding the risks of ambrisentan and agree to comply with the requirements of the Ambrisentan REMS
 - Complete the form online at www.ambrisentanrems.us.com or fax the completed form to 1-866-750-9802
3. Determine the reproductive status of female patients

Females of Reproductive Potential:

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below)
- For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non-Reproductive Potential:

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-Menopausal Females: Females who have passed through Menopause (as defined below)
- Females with other medical reasons for permanent, irreversible infertility

Definition of Menopause:

- Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy

4. Educate/counsel all female patients about the risks of ambrisentan and about the Ambrisentan REMS
 - Advise all females that ambrisentan is only available through a restricted distribution program called the Ambrisentan REMS

For Females of Reproductive Potential:

- Review the *Guide for Female Patients* prior to initiating treatment
- Counsel the patient about the risk of embryo-fetal toxicity, the need to use highly reliable contraception (see page 6) during ambrisentan treatment and for one month following treatment discontinuation, and the need to use emergency contraception using the *Guide for Female Patients*
- Assess the patient's pregnancy status by ordering and reviewing pregnancy tests prior to initiation of ambrisentan treatment, monthly during treatment, and for one month following treatment discontinuation
- Advise the patient of the requirement for monthly pregnancy tests to confirm they are not pregnant so they can receive ambrisentan
- Counsel if she is not complying with the required testing of if she is not using appropriate contraception
- Submit a ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** within 10 business days of becoming aware of any change in reproductive status
- Prescribe no more than a 30 days' supply at a time
- Notify the Ambrisentan REMS if any patient becomes pregnant during ambrisentan treatment or within one month following treatment discontinuation

For Females of Non-Reproductive Potential:

For Pre-Pubertal Females:

- Review the *Guide for Female Patients* prior to initiating treatment
- Counsel the patient and parent/guardian about the risk of embryo-fetal toxicity using the *Guide for Female Patients*
- Evaluate regularly for any changes in reproductive status while receiving ambrisentan
- Verify the reproductive status annually for Pre-Pubertal Females who are at least 8 years of age and older by completing and submitting the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***
- Report a change or misclassification in reproductive status by completing and submitting the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** within 10 business days of becoming aware of the change
- Notify the Ambrisentan REMS if any patient becomes pregnant during ambrisentan treatment or within one month following treatment discontinuation

For Post-Menopausal Females:

- Review the *Guide for Female Patients* prior to initiating treatment
- Report a change or misclassification in reproductive status by completing and submitting the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** within 10 business days of becoming aware

For females with other medical reasons for permanent, irreversible infertility:

- Review the *Guide for Female Patients* prior to initiating treatment
- Report a change or misclassification in reproductive status by completing and submitting the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** within 10 business days of becoming aware

5. Check pregnancy status in Female of Reproductive Potential

- Order and review pregnancy test results for the patient:
 - Prior to initiating treatment
 - Monthly during treatment
 - One month following treatment discontinuation

The patient must agree to be contacted by the certified pharmacy prior to each shipment to confirm that a pregnancy test was completed, and she must also agree to be contacted by the Ambrisentan REMS if she becomes pregnant while on ambrisentan or within one month of stopping treatment.

6. Enroll all female patients into the Ambrisentan REMS

- Complete and submit the *Patient Enrollment Form* via fax to 1-866-750-9802 or login to complete and submit online at www.ambrisentanrems.us.com.
- Keep the original form with the patient's records

7. Evaluate reproductive status of female patients throughout treatment

- Report a change or misclassification in reproductive status to the Ambrisentan REMS within 10 business days of becoming aware of the change by faxing the completed ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** to 1-866-750-9802 or online at www.ambrisentanrems.us.com. Verify the reproductive status of Pre-Pubertal Females who are at least 8 years of age or older annually by completing and submitting the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***
- Counsel females who fail to comply with the Ambrisentan REMS requirements
- Notify the Ambrisentan REMS if any patient becomes pregnant during ambrisentan treatment or within one month following treatment discontinuation

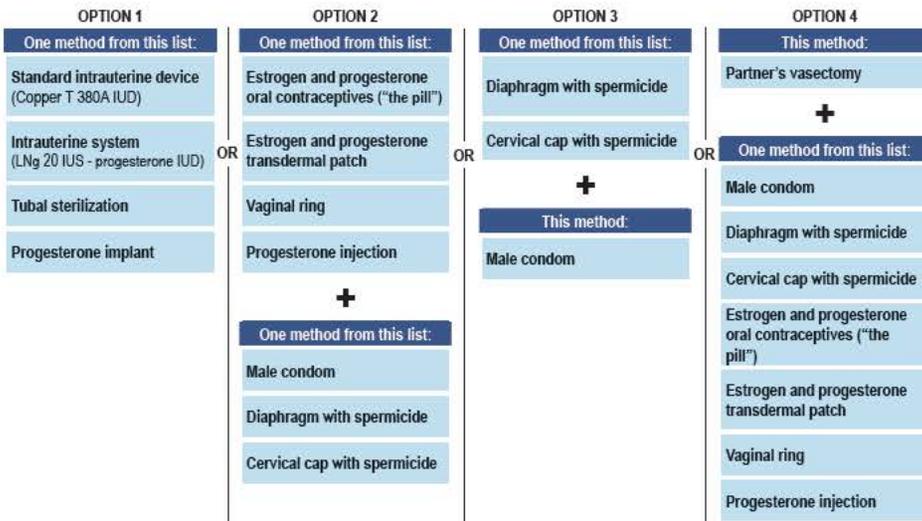
Contraceptive Options for Females of Reproductive Potential

All Females of Reproductive Potential should undergo contraceptive counseling with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.

Please refer to the diagram below for a complete list of the acceptable contraceptive options. The same diagram also appears in the **Guide for Female Patients** and should be used to discuss acceptable birth control options with patients.

- Educate and counsel Females of Reproductive Potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure
- Remind patients to report to you immediately any delay in having a period or any other reason of suspected pregnancy during treatment
- If pregnancy is suspected for any reason, a pregnancy test must be performed
- **The prescriber must notify the Ambrisentan REMS of any pregnancies that occur during treatment or within one month following treatment discontinuation**

Contraceptive Options for Females of Reproductive Potential



Role of Certified Pharmacies

Outpatient Pharmacy Dispensing:

Only a limited number of certified pharmacies will dispense ambrisentan for outpatients. In order for patients to receive ambrisentan, all outpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the program.

Prior to dispensing, the outpatient pharmacy must:

- For Females of Reproductive Potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception and emergency contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.
- Verify with the Ambrisentan REMS that the patient's prescriber is enrolled for all patients and if the patient is female, verify the patient is enrolled and the reproductive status has not changed.
- For Females of Reproductive Potential: Verify that the pregnancy testing is complete or the prescriber authorizes the refill.
- For Females of Reproductive Potential: Dispense no more than a 30 days' supply.

At all times, the outpatient pharmacy must:

- Report pregnancies to the Ambrisentan REMS.
- Report a change or misclassification in reproductive status to the Ambrisentan REMS.
- Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
- Maintain and submit records of daily product dispensing data for female patients to the Ambrisentan REMS.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

Inpatient Pharmacy Dispensing:

Only inpatient pharmacies within institutions such as hospitals, long-term care facilities, and prisons that are certified in the Ambrisentan REMS may stock ambrisentan for patients being treated in the inpatient setting. In order for inpatients to receive ambrisentan, all inpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the program.

Prior to dispensing, the inpatient pharmacy must:

- Verify with the Ambrisentan REMS that the patient's prescriber is enrolled for all patients and if the patient is female verify the patient is enrolled.
- For Females of Reproductive Potential: Verify that the patient has been counseled on the risk of embryo-fetal toxicity and pregnancy testing is complete.

Prior to discharge of a patient, the inpatient pharmacy must:

- Dispense no more than a 15 days' supply upon discharge.

At all times, the inpatient pharmacy must:

- Report pregnancies to the Ambrisentan REMS.
- Report a change or misclassification in reproductive status to the Ambrisentan REMS.
- Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

For a list of Certified Pharmacies, call the Ambrisentan REMS at 1-888-417-3172

The Ambrisentan REMS

- Enters every ambrisentan prescriber, female patient, and enrolled pharmacy into the Ambrisentan REMS database
- Collects all **Patient Enrollment Forms**, **Prescriber Enrollment Forms**, **Pharmacy Enrollment Forms (Outpatient and Inpatient)**, and **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms**
- Allow access to the certified pharmacies for verification of patient and prescriber information
- Collects information about changes in reproductive status, annual verification of reproductive status for Pre-Pubertal Females, and any occurrences of pregnancies during ambrisentan treatment or within one month following treatment discontinuation

Ambrisentan REMS Prescriber Enrollment and Agreement Form

To enroll in the Ambrisentan REMS, complete and fax this form to 1-866-750-9802 or complete and submit online at www.ambrisentanrems.us.com

| 1 Prescriber Information (PLEASE PRINT) | | | |
|---|-----------------------|------------|-------|
| First Name: | Middle Initial: | Last Name: | |
| Suffix: | | | |
| Specialty: | Name of Facility: | | |
| Office Contact (First and Last Name): | | | |
| Address: | City: | State: | Zip: |
| Email: | Phone: | Fax: | |
| State License #: | NPI #: | | |
| 2 Prescriber Agreement | | | |
| By signing below, you attest to the following: | | | |
| <ul style="list-style-type: none">I have reviewed the Prescribing Information and the Prescriber and Pharmacy Guide and agree to comply with the REMS requirements.I will enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS. | | | |
| For all females: | | | |
| <ul style="list-style-type: none">I will determine the reproductive potential status of all female patients using the definitions provided in the Prescriber and Pharmacy Guide and document and submit the results to the REMS using the Patient Enrollment Form.I will counsel all female patients that ambrisentan is only available through a restricted distribution program called the Ambrisentan REMS.I will enroll all female patients by completing and submitting the Patient Enrollment Form. | | | |
| For females of reproductive potential: | | | |
| <ul style="list-style-type: none">I will counsel Females of Reproductive Potential about the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, and emergency contraception using the Guide for Female Patients.I will assess the pregnancy status of Females of Reproductive Potential by ordering and reviewing a pregnancy test before treatment initiation, before writing each prescription, and for one month after treatment discontinuation.I will counsel Females of Reproductive Potential if they are not complying with the required testing or if they are not using appropriate contraception. | | | |
| Pre-pubertal females: | | | |
| <ul style="list-style-type: none">I will counsel each Pre-Pubertal Female patient and her parent/guardian on the risk of embryo-fetal toxicity using the Guide for Female Patients.I will regularly assess the reproductive status of each Pre-Pubertal Female during their treatment with ambrisentan.I will assess the reproductive status for Pre-Pubertal Females who are 8 years of age and older and will document and submit findings to the REMS at least annually using the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form. | | | |
| At all times: | | | |
| <ul style="list-style-type: none">I will report any change or misclassification in reproductive status to the Ambrisentan REMS using Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form within 10 business days of becoming aware of the change in reproductive status.I will report pregnancies to the REMS. | | | |
| REQUIRED | Prescriber Signature: | | Date: |

Please visit www.ambrisentanrems.us.com or call 1-888-417-3172 for more information about the Ambrisentan REMS.

This form is part of an FDA-approved REMS.

Ambrisentan REMS Patient Enrollment and Consent Form

To enroll in the Ambrisentan REMS, complete and fax this form to 1-866-750-9802 or complete and submit online at www.ambrisentanrems.us.com

| 1 Patient Information (PLEASE PRINT) | | | |
|--|---|--|------------------|
| First Name: | Middle Initial: | Last Name: | |
| Address: | City: | State: | Zip: |
| Birthdate: / / | Gender: <input type="checkbox"/> Female | Preferred time to contact: <input type="checkbox"/> Day <input type="checkbox"/> Evening | |
| Home Phone: | Mobile Phone: | E-mail: | |
| Alternate Contact Name: | | Alternate Phone: | |
| Relationship: | | | |
| 2 Female Patient Agreement | | | |
| For Females Who Can Get Pregnant: | | | |
| Before I begin ambrisentan treatment I will: | | | |
| <ul style="list-style-type: none">Review the Guide for Female Patients.Get a pregnancy test.Enroll in the REMS by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS.Receive counseling from the prescriber on the risk of serious birth defects, the need to use highly reliable contraception during treatment and for one month after stopping treatment, and emergency contraception using the Guide for Female Patients. | | | |
| Before I receive each prescription of ambrisentan I will: | | | |
| <ul style="list-style-type: none">Receive counseling from the pharmacy or prescriber on risk of serious birth defects and the need to use highly reliable contraception during treatment and for one month after stopping treatment, emergency contraception, to get monthly pregnancy tests, and to report a pregnancy immediately.Get a pregnancy test.Communicate with the pharmacy to confirm pregnancy testing. | | | |
| During my treatment with ambrisentan and for one month after stopping treatment, I will: | | | |
| <ul style="list-style-type: none">Use highly reliable contraception as described in the Guide for Female Patients.Get a pregnancy test monthly during treatment and for one month after I stop taking ambrisentan.Agree to be contacted by the REMS to obtain information about my pregnancy if I become pregnant while on ambrisentan or within 30 days after stopping treatment. | | | |
| For Pre-Pubertal Females (and their parent/guardian): | | | |
| Before I begin ambrisentan treatment, I will: | | | |
| <ul style="list-style-type: none">Review the Guide for Female Patients.Enroll in the REMS by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS.Receive counseling from the prescriber on the risk of serious birth defects using the Guide for Female Patients. | | | |
| If I am over the age of 8 and while I am being treated with ambrisentan, I will be monitored regularly for a change in reproductive status. | | | |
| I will tell my prescriber if my reproductive status (ability to become pregnant) changes. | | | |
| For Post-menopausal Females or Females with other medical reasons for permanent, irreversible infertility: | | | |
| Before I begin ambrisentan treatment, I will: | | | |
| <ul style="list-style-type: none">Review the Guide for Female Patients.Enroll in the REMS by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS. | | | |
| I will tell my prescriber if my reproductive status (ability to become pregnant) changes. | | | |
| REQUIRED FOR ALL FEMALE PATIENTS | Patient or Parent/Guardian Signature: | | Date: |
| 3 Prescriber Information (PLEASE PRINT) | | | |
| First Name: | Last Name: | | State License #: |
| Address: | City: | State: | Zip: |
| Phone: | Fax: | NPI#: | |
| Office Contact (First and Last Name): | | | E-mail: |

4 Statement of Medical Necessity

Diagnosis: Pulmonary Arterial Hypertension (The following list is not to suggest approved uses or indications. Please select one category below.)

ICD-10 I27.0 Primary Pulmonary Hypertension

- Idiopathic PAH
- Heritable PAH

ICD-10 I27.21 Secondary Pulmonary Arterial Hypertension

- Connective tissue disease
- Congenital heart disease with repaired shunts
- Other (please specify): _____

5 Prescriber Authorization (REQUIRED FOR ALL FEMALE PATIENTS)

Only 1 box should be checked. For female patients, please indicate the patient's current reproductive status below. (Please see definitions of these terms below)

Female of Reproductive Potential

Has a negative pregnancy test been confirmed prior to prescribing ambrisentan?

- Yes
- No

OR

Female of Non-Reproductive Potential (choose one below)

- Pre-Pubertal Female
- Post-Menopausal Female
- Other medical reasons for permanent, irreversible infertility

I certify that for female patients, I have provided the appropriate counseling and REMS materials, and I will continue to fulfill my obligations under the REMS.

REQUIRED
FOR ALL
PRESCRIBERS

Prescriber Signature: _____

Date: _____

Definitions

Females of Reproductive Potential

- Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).
- For the purposes of REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal).

Females of Non-Reproductive Potential

- Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.
- Post-Menopausal Females: Females who have passed through Menopause (as defined below).
- Other medical reasons for permanent, irreversible infertility.

Menopause

Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or postsurgical from bilateral oophorectomy.

Prescriber obligations under the REMS

For All Females

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that ambrisentan is available only through a restricted distribution program under an FDA-required REMS.
- I will evaluate the patient and agree to document any change in reproductive potential status by submitting a **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form** within 10 business days of becoming aware of the change.

For Females of Reproductive Potential

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of ambrisentan, including the risk of serious birth defects, and that I have reviewed the **Guide for Female Patients** with the patient (and parent/guardian when appropriate).
- I will order and review pregnancy tests prior to initiation of ambrisentan treatment, monthly during treatment, and for 1 month following treatment discontinuation in accordance with the REMS.

For Pre-Pubertal Females

- I acknowledge that I have counseled the patient and parent/guardian on the risks of ambrisentan, including the risk of serious birth defects, and that I have reviewed the **Guide for Female Patients** with the patient (and parent/guardian when appropriate).
- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-Pubertal Females who are at least 8 years of age and older, and agree to report any change in reproductive potential status on a **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form** within 10 business days of becoming aware of the change.

6 Complete and fax this enrollment form to 1-866-750-9802 or complete and submit the form online at www.ambrisentanrems.us.com.

Please visit www.ambrisentanrems.us.com or call 1-888-417-3172 for more information about the Ambrisentan REMS.

This form is part of an FDA-approved REMS.

AMBRISENTAN RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Ambrisentan REMS **GUIDE FOR FEMALE PATIENTS**

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Information for Females Patients

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This guide is part of an FDA-approved REMS.

Information for Females

What is Ambrisentan?

Ambrisentan is a prescription medicine used to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Ambrisentan can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

What are the serious risks of Ambrisentan?

Ambrisentan can cause serious birth defects if taken during pregnancy. Females must not be pregnant when they start taking ambrisentan or become pregnant while taking ambrisentan, or for one month after stopping ambrisentan.

What is the Ambrisentan Risk Evaluation and Mitigation Strategy (REMS)?

Because of the risk of serious birth defects, the FDA has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for ambrisentan. The purpose of the Ambrisentan REMS is to make sure the benefits of ambrisentan outweigh the risks. All females must enroll in the Ambrisentan REMS to receive ambrisentan. Specific requirements apply to females who can get pregnant.

To receive Ambrisentan:

| | | | |
|---|--|---|--|
| 1) You must talk with your doctor to ensure the benefits outweigh the risks of ambrisentan | 2) You must agree to all of the requirements of the Ambrisentan REMS. These requirements include monthly pregnancy tests and use of appropriate birth control for females that can get pregnant while taking ambrisentan and for one month after stopping ambrisentan | 3) Your doctor will enroll you in the Ambrisentan REMS | 4) Your prescription will be mailed to you from a certified pharmacy that you and your doctor will choose |
|---|--|---|--|

How do I enroll in the Ambrisentan REMS?

Follow these steps with your doctor:

- ✓ Read all the patient information about ambrisentan and the Ambrisentan REMS included in this guide or on the Ambrisentan REMS website, www.ambrisentanrems.us.com
- ✓ Talk with your doctor to ensure the benefits outweigh the risks of ambrisentan
- ✓ Ask questions. Make sure you understand what you need to do to enroll and take part in the Ambrisentan REMS. Make sure you know how to receive and take ambrisentan
- ✓ You and your doctor choose a certified pharmacy to supply ambrisentan. In some cases, your insurance company may need you to use a specific certified pharmacy
- ✓ You and your doctor fill out the *Patient Enrollment Form*. After you read and sign it, your doctor sends it to the Ambrisentan REMS

What are the Ambrisentan REMS requirements for me?

Females Who Cannot Get Pregnant:

You are considered a female who cannot get pregnant if you have not yet entered puberty, or you do not have a uterus, or you have gone through menopause, or you are infertile for any other medical reason and this infertility is permanent and cannot be reversed.

To receive ambrisentan, you must:

- Enroll in the Ambrisentan REMS by completing the *Patient Enrollment Form*
- Receive counseling from your prescriber on the risk of serious birth defects (Pre-pubertal females only)
- Tell your prescriber if you become pregnant or your ability to become pregnant changes
- If you are over the age of 8: Be monitored every year to see if your ability to become pregnant changes and tell your prescriber if your ability to become pregnant changes
 - Agree to be contacted by the Ambrisentan REMS if you become pregnant while on ambrisentan or within one month of stopping treatment.
 - If you are the parent or caregiver of a female child who started taking ambrisentan before reaching puberty, you should check your child regularly to see if she is developing signs of puberty. Tell your doctor right away if you notice that she is developing breast buds or pubic hair. Your doctor should decide if your child has reached puberty. **Your child may reach puberty before having her first menstrual period.**

Females Who Can Get Pregnant:

You are considered to be a female who can get pregnant if you have entered puberty, have a uterus, and have not gone through menopause.

To receive ambrisentan, you must:

- Enroll in the Ambrisentan REMS by completing the *Patient Enrollment Form*.
- Have a negative pregnancy test before you start taking ambrisentan and before you receive your refills. Your doctor orders the pregnancy tests for you. Your certified pharmacy will call you and ask if you have taken this test before shipping your refill.
- **Be sure you take your monthly pregnancy test as ordered by your doctor. Your certified pharmacy may call you and ask if you have taken this test before shipping your refill. If you do not take your pregnancy test every month, you may not receive your ambrisentan on time.**
- Agree to be contacted by the Ambrisentan REMS if you become pregnant while on ambrisentan or within one month of stopping treatment.

Do not have unprotected sex (intercourse). Use appropriate birth control during your ambrisentan treatment and for one month after stopping your ambrisentan treatment because the medicine may still be in your body. Page 4 of this guide shows your birth control options.

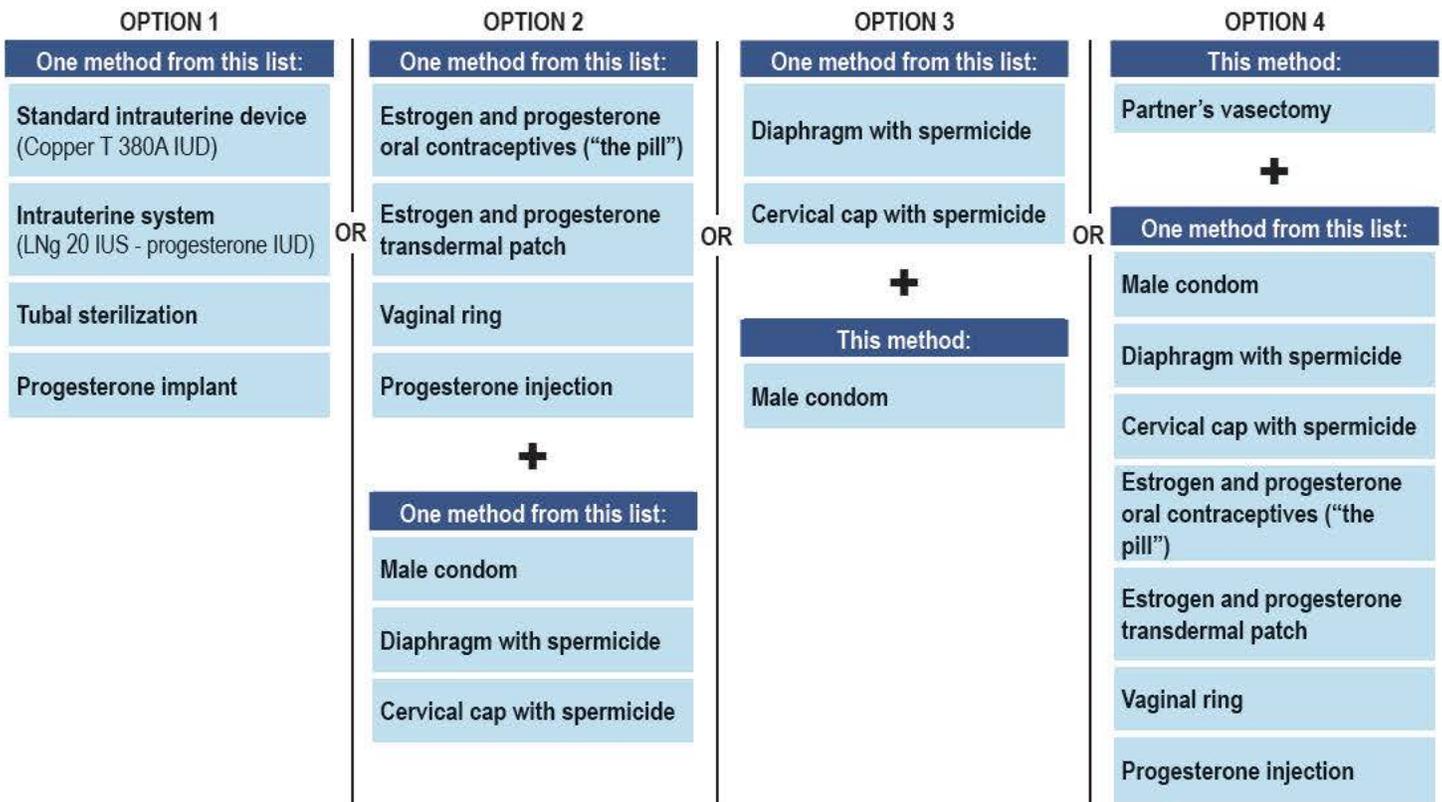
Talk to your doctor or pharmacist right away if you have unprotected sex, if you think your birth control has failed, or if you think you may be pregnant. Your doctor may tell you to use emergency birth control. Do not wait until your next appointment to tell your doctor if you miss your menstrual period or if you think you may be pregnant.

What are my birth control options?

If you are a female who can get pregnant, your doctor will talk to you about your birth control options. Use the diagram on the next page to help decide what birth control options are best for you. Talk to your doctor if you have questions about your birth control options. Tell your doctor if you want to change your birth control method.

You may choose from the four options listed on the next page. More than one birth control method might be needed every time you have sex.

Your birth control options



How will I receive my Ambrisentan?

Certified pharmacies provide products and services for patients with certain diseases. Only certified pharmacies can provide ambrisentan to you. In some cases, your insurance company may require you to use a specific certified pharmacy.

Your certified pharmacy ships your ambrisentan refill to you. Before each shipment, you will be called to confirm that you have taken a monthly pregnancy test before refilling your prescription. **It is important that your certified pharmacy is able to contact you in order to avoid delays in your refills.**

If you have questions or concerns about ambrisentan, talk to your doctor. Please visit www.ambrisentanrems.us.com or call 1-888-417-3172 for more information about the Ambrisentan REMS.

Ambrisentan REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form

Complete and fax this form to: 1-866-750-9802 or complete and submit online at www.ambrisentanrems.us.com

Complete this form to:

1. Change the reproductive status of any female patient, or
2. Complete the annual verification of reproductive potential status for Pre-Pubertal Females, 8 years of age or older

Prescriber must complete this form within 10 business days of awareness of the change in reproductive potential status.

| 1 Patient Information (PLEASE PRINT) | | | |
|---|--|------------------|-------|
| Patient Ambrisentan REMS ID: | | | |
| First Name: | Middle Initial: | Last Name: | |
| Address: | City: | State: | Zip: |
| Birthdate: / / | Phone: | | |
| 2 Prescriber Information (PLEASE PRINT) | | | |
| Office Contact and E-mail Address: | | | |
| First Name: | Last Name: | State License #: | |
| Address: | City: | State: | Zip: |
| Phone: | Fax: | NPI #: | |
| Definitions of Reproductive Potential Status: | | | |
| <u>Females of Reproductive Potential</u> | | | |
| <ul style="list-style-type: none">• Females of Reproductive Potential include girls who have entered puberty and all women who have a uterus and have not passed through Menopause (as defined below).• For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal). | | | |
| <u>Females of Non-Reproductive Potential</u> | | | |
| <ul style="list-style-type: none">• Pre-Pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential.• Post-Menopausal Female: Females who have passed through Menopause (as defined below).• Other medical reasons for permanent, irreversible infertility. | | | |
| <u>Menopause</u> | | | |
| Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy. | | | |
| 3 Please select the most appropriate reason for submitting this form. | | | |
| Change in Status | | | |
| <ul style="list-style-type: none">• Based on definitions of reproductive potential status, patient is (please check one):<ul style="list-style-type: none"><input type="checkbox"/> Female of Reproductive Potential<input type="checkbox"/> Female of Non-Reproductive Potential – Patient is pre-pubertal<input type="checkbox"/> Female of Non-Reproductive Potential – Patient is post-menopausal<input type="checkbox"/> Female of Non-Reproductive Potential – Other medical reasons for permanent, irreversible infertility• Reason for change in classification (please check one):<ul style="list-style-type: none"><input type="checkbox"/> Physiological transition<input type="checkbox"/> Medical/surgical (please specify): _____<input type="checkbox"/> Other (please specify): _____ | | | |
| Annual Verification | | | |
| <input type="checkbox"/> Patient remains a Pre-Pubertal Female (8 years of age or older) | | | |
| REQUIRED | By signing, I certify that the patient's reproductive potential status and reason for submitting this form are accurately noted above. | | Date: |
| | Prescriber Signature: | | |

Please visit www.ambrisentanrems.us.com or call 1-888-417-3172 for more information about the Ambrisentan REMS.

This form is part of an FDA-approved REMS.

Ambrisentan REMS Outpatient Pharmacy Enrollment Form

To enroll in the Ambrisentan REMS, complete and fax this form to 1-866-750-9802

Due to the risk of embryo-fetal toxicity, ambrisentan is available only through a restricted program called the Ambrisentan REMS (Risk Evaluation and Mitigation Strategy). In order for patients to receive ambrisentan, all outpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the program.

An Authorized Representative must be designated to carry out the certification process and oversee implementation of and compliance with the REMS on behalf of the pharmacy. As the authorized representative, complete and submit this form on behalf of your outpatient pharmacy.

If you have any questions, require additional information, or need further copies of REMS materials, please visit the REMS website at www.ambrisentanrems.us.com, or call the Ambrisentan REMS at 1-888-417-3172.

Outpatient Pharmacy Information (PLEASE PRINT)

Pharmacy Name:

Identification (please complete one of the following):

Facility Health Industry Number (HIN #):

Facility National Provider Identifier (NPI #):

Other identifier:

Address:

City:

State:

Zip:

Phone #:

Fax #:

Ship To Address (if different from above)

Address:

City:

State:

Zip:

Phone #:

Fax #:

Outpatient Pharmacy Authorized Representative Information (PLEASE PRINT)

Name:

Position/Title:

Credentials: RPh PharmD BCPS Other

Authorized Representative phone #:

Fax #:

Authorized Representative email:

Contact Preference (please select one) Email Fax

Outpatient Pharmacy Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to coordinate the activities of the REMS.

Therefore, I must:

- Carry out the certification process and oversee implementation of and compliance with the REMS on behalf of the pharmacy.
- Review the **Prescriber and Pharmacy Guide**.
- Enroll in the REMS by completing and submitting the **Outpatient Pharmacy Enrollment Form**.
- Train all relevant staff involved in dispensing ambrisentan on REMS procedures and materials using the **Prescriber and Pharmacy Guide**.
- Ensure the pharmacy is able to support electronic data exchanges and communications with the Ambrisentan REMS.
- Establish processes and procedures to verify if the female patient is enrolled, the reproductive status of the patient has not changed, and the prescriber is certified.
- Establish processes and procedures to verify that pregnancy testing is complete or the prescriber authorizes the refill for females of reproductive potential.

On behalf of the pharmacy, I agree to comply with the following program requirements:

Prior to dispensing, the outpatient pharmacy must:

- Counsel females of reproductive potential on the risk of embryo-fetal toxicity, the need to use highly reliable contraception, emergency contraception, to get monthly pregnancy tests, and inform the prescriber of a pregnancy immediately.
- Verify the female patient is enrolled, the reproductive status has not changed, and the prescriber is certified through the processes and procedures established as a requirement of the REMS.
- For females of reproductive potential, verify that the pregnancy testing is complete or the prescriber authorizes the refill through the processes and procedures established as a requirement of the REMS.
- Dispense no more than a 30 days' supply for females of reproductive potential.

At all times, the outpatient pharmacy must:

- Report pregnancies to the REMS.
- Report a change or misclassification in reproductive status to the REMS.
- Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
- Maintain and submit records of daily product dispensing data for female patients of reproductive potential.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

Outpatient Pharmacy Authorized Representative Consent

By signing below, you signify your understanding of the risks of ambrisentan treatment, your obligations as a pharmacy certified in the REMS as outlined above, and you agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy.

Note: If your outpatient pharmacy needs ambrisentan and is not enrolled in the REMS, contact the Ambrisentan REMS at 1-888-417-3172 for assistance in initiating enrollment of the pharmacy.

Signature:

Date:

Please visit www.ambrisentanrems.us.com or call 1-888-417-3172 for more information about the Ambrisentan REMS Program.
This form is part of an FDA-approved REMS.

Ambrisentan REMS Inpatient Pharmacy Enrollment Form

To enroll in the Ambrisentan REMS, complete and fax this form to 1-866-750-9802 or complete and submit online at www.ambrisentanrems.us.com

Due to the risk of embryo-fetal toxicity, ambrisentan is available only through a restricted program called the Ambrisentan REMS (Risk Evaluation and Mitigation Strategy). In order for inpatients to receive ambrisentan, all inpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the program.

An Authorized Representative must be designated to carry out the certification process and oversee implementation of and compliance with the REMS on behalf of the pharmacy. As the authorized representative, complete and submit this form on behalf of your inpatient pharmacy.

If you have any questions, require additional information, or need further copies of REMS materials, please visit the REMS website at www.ambrisentanrems.us.com, or call the Ambrisentan REMS at 1-888-417-3172.

Inpatient Pharmacy Information (PLEASE PRINT)

Pharmacy Name:

Hospital Nursing home Hospice Asylum/Mental facility Assisted Living Prison Rehabilitation

Other (Please specify):

Identification (please complete one of the following):

Facility Health Industry Number (HIN #): Facility National Provider Identifier (NPI #): Other identifier:

Address:

City: State: Zip:

Phone #: Fax #:

Ship To Address (if different from above)

Address:

City: State: Zip:

Phone #: Fax #:

Inpatient Pharmacy Authorized Representative Information (PLEASE PRINT)

Name: Position/Title: Hospital pharmacist Head of Pharmacy and Therapeutics (P&T) committee
 Other title:

Credentials: RPh PharmD BCPS Other

Authorized Representative phone #: Fax #:

Authorized Representative email:

Contact Preference (please select one) Email Fax

Inpatient Pharmacy Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to coordinate the activities of the REMS. Therefore, I must:

- Carry out the certification process and oversee implementation of and compliance with the REMS on behalf of the pharmacy.
 - Review the **Prescriber and Pharmacy Guide**.
 - Enroll in the REMS by completing and submitting the **Inpatient Pharmacy Enrollment Form**.
 - Train all relevant staff involved in dispensing ambrisentan on REMS procedures and materials using the **Prescriber and Pharmacy Guide**.
 - Establish processes and procedures to verify the female patient is enrolled or will be enrolled in the REMS prior to discharge, her reproductive status, and the female patient is under the supervision and care of a certified provider.
 - For females of reproductive potential: establish processes and procedures to verify pregnancy testing is complete, and the patient is counseled on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month after stopping treatment, emergency contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.
- reproductive status, and she is enrolled or will be enrolled in the REMS prior to discharge through the processes and procedures established as a requirement of the REMS.
- For females of reproductive potential: Verify that the pregnancy testing is complete, the patient is counseled on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month after stopping treatment, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately through the processes and procedures established as a requirement of the REMS.

At discharge of a patient, the inpatient pharmacy must:

- Dispense no more than a 15 days' supply.

At all times, the inpatient pharmacy must:

- Report pregnancies to the REMS.
- Report a change or misclassification in reproductive status to the REMS.
- Not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

On behalf of the pharmacy, I agree to comply with the following program requirements:

Prior to dispensing, the inpatient pharmacy must:

- Verify the female patient is under the supervision and care of a certified prescriber, her

Inpatient Pharmacy Authorized Representative Consent

By signing below, you signify your understanding of the risks of ambrisentan treatment, your obligations as a pharmacy certified in the REMS as outlined above, and you agree to oversee the implementation of and compliance with the REMS requirements for this pharmacy.

Note: If your inpatient pharmacy needs ambrisentan and is not enrolled in the REMS, contact the REMS at 1-888-417-3172 for assistance in initiating enrollment of the pharmacy.

Signature:

Date:

Please visit www.ambrisentanrems.us.com or call 1-888-417-3172 for more information about the Ambrisentan REMS Program.

This form is part of an FDA-approved REMS.

REMS Changes



The Ambrisentan REMS is a shared system REMS for approved ambrisentan products associated with this REMS, including Letairis, replacing the Letairis REMS Program. Prescribers currently certified and patients currently enrolled in the Letairis REMS Program will be transitioned from the Letairis REMS Program to the Ambrisentan REMS without the requirement to recertify or reenroll in the Ambrisentan REMS. Currently certified outpatient pharmacies in the Letairis REMS Program that are transitioning to the Ambrisentan REMS will be required to recertify in the Ambrisentan REMS.

CLOSE

The Ambrisentan REMS (Risk Evaluation and Mitigation Strategy)

The Ambrisentan REMS is a safe and effective system designed to ensure that the benefits of ambrisentan outweigh the risks. The Ambrisentan REMS is required by the FDA for the safe use of ambrisentan.

- Only prescribers and pharmacies certified by the Ambrisentan REMS can prescribe or dispense ambrisentan.
- Patients must be enrolled in the Ambrisentan REMS before starting ambrisentan.

ing ambrisentan. The

Prescribers

Click here to learn how to prescribe ambrisentan

To prescribe ambrisentan:

- 1 Review the Prescribing Information and *Prescriber and Pharmacy Guide*

- 2 Enroll in the REMS by completing

Female Patients

Click here to learn how to receive ambrisentan

To receive ambrisentan:

- 1 Review the *Guide for Female Patients*
- 2 Receive counseling from your prescriber to understand the risks

Outpatient Pharmacies

Click here to learn how to dispense ambrisentan

To dispense ambrisentan:

- 1 Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Ambrisentan REMS on Letairis/Ambrisentan

Inpatient Pharmacies

Click here to learn how to dispense ambrisentan

To dispense ambrisentan:

- 1 Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Ambrisentan REMS on Letairis/Ambrisentan

The Ambrisentan REMS (Risk Evaluation and Mitigation Strategy)

The Ambrisentan REMS is a safety program that manages the risk of serious birth defects when taking ambrisentan. The Ambrisentan REMS is required by the Food and Drug Administration (FDA).

- Only prescribers and pharmacies certified by the Ambrisentan REMS can prescribe and dispense ambrisentan to patients.
- Patients must be enrolled in the Ambrisentan REMS and follow all the safety rules in the REMS in order to receive ambrisentan.

| Prescribers | Female Patients | Outpatient Pharmacies | Inpatient Pharmacies |
|---|---|--|---|
| <p>Click here to learn how to prescribe ambrisentan</p> <p>To prescribe ambrisentan:</p> <ol style="list-style-type: none"> 1 Review the Prescribing Information and <i>Prescriber and Pharmacy Guide</i> 2 Enroll in the REMS by completing the <i>Prescriber Enrollment Form</i> and submitting it to the Ambrisentan REMS 3 Assess the patient's reproductive status as defined in the <i>Prescriber and Pharmacy Guide</i> 4 Enroll all females in the Ambrisentan REMS by completing and submitting the <i>Patient Enrollment Form</i> to the Ambrisentan REMS 5 Report any changes in the reproductive status of a female patient via the <i>Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form</i> | <p>Click here to learn how to receive ambrisentan</p> <p>To receive ambrisentan:</p> <ol style="list-style-type: none"> 1 Review the <i>Guide for Female Patients</i> 2 Receive counseling from your prescriber to understand the risks associated with ambrisentan 3 Enroll in the Ambrisentan REMS by completing the <i>Patient Enrollment Form</i> with your healthcare provider 4 For females who can get pregnant: <ul style="list-style-type: none"> • Complete a monthly pregnancy test and use appropriate birth control while taking ambrisentan and for one month after treatment discontinuation 5 For females who cannot get pregnant: <ul style="list-style-type: none"> • Tell your healthcare provider if you become pregnant or your ability to become pregnant changes • If you are over the age of 50 be monitored every year to see if your ability to become pregnant changes and tell your healthcare provider if your ability to become pregnant changes 6 Report changes in reproductive status to your healthcare provider | <p>Click here to learn how to dispense ambrisentan</p> <p>To dispense ambrisentan:</p> <ol style="list-style-type: none"> 1 Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Ambrisentan REMS on behalf of the pharmacy 2 Have the authorized representative enroll in the Ambrisentan REMS by completing the <i>Outpatient Pharmacy Enrollment Form</i> and submitting it to the Ambrisentan REMS 3 Train staff involved in dispensing ambrisentan and comply with Ambrisentan REMS requirements 4 Obtain authorization to dispense each prescription by contacting the Ambrisentan REMS online or by phone to verify the patient's prescriber is enrolled for all patients and if the patient is female, verify the patient is enrolled <ul style="list-style-type: none"> • For females of Reproductive Potential (RP): <ul style="list-style-type: none"> • Dispense no more than a 30-day* supply 5 Support electronic data exchanges and communication with the Ambrisentan REMS system | <p>Click here to learn how to dispense ambrisentan</p> <p>To dispense ambrisentan:</p> <ol style="list-style-type: none"> 1 Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Ambrisentan REMS on behalf of the pharmacy 2 Have the authorized representative enroll in the Ambrisentan REMS by completing the <i>Inpatient Pharmacy Enrollment Form</i> and submitting it to the Ambrisentan REMS 3 Train staff involved in dispensing ambrisentan and comply with Ambrisentan REMS requirements 4 Obtain authorization to dispense each prescription by contacting the Ambrisentan REMS online or by phone to verify the patient's prescriber is enrolled for all patients and if the patient is female, verify the patient is enrolled <ul style="list-style-type: none"> • Dispense no more than a 15-day* supply at discharge |

PDFs for Download

| Resources for Prescribers | Resources for Female Patients | Resources for Outpatient Pharmacies | Resources for Inpatient Pharmacies |
|---|--|--|---|
| <ul style="list-style-type: none"> Ambrisentan REMS Prescriber and Pharmacy Guide Ambrisentan REMS Prescriber Enrollment and Agreement Form Ambrisentan REMS Patient Enrollment and Consent Form Ambrisentan REMS Guide for Female Patients Ambrisentan REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form | <ul style="list-style-type: none"> Ambrisentan REMS Guide for Female Patients | <ul style="list-style-type: none"> Ambrisentan REMS Outpatient Pharmacy Enrollment Form Ambrisentan REMS Prescriber and Pharmacy Guide | <ul style="list-style-type: none"> Ambrisentan REMS Inpatient Pharmacy Enrollment Form Ambrisentan REMS Prescriber and Pharmacy Guide |

Click here for a list of approved products covered under the Ambrisentan REMS

To learn more about the serious risks associated with ambrisentan, please refer to the US Prescribing Information including Boxed Warning, Ambrisentan REMS Prescriber and Pharmacy Guide and Ambrisentan REMS Guide for Female Patients.

List of products covered under the Ambrisentan REMS

Brand:

| Brand Name | Generic Name | Dosage | Company | Contact | Links |
|------------|--------------|--------|---------|---------|---|
| | | | | | Prescribing Information |
| | | | | | Prescribing Information |

Generic:

| Drug Name | Dosage | Company | Contact | Links |
|-----------|--------|---------|---------|---|
| | | | | Prescribing Information |
| | | | | Prescribing Information |

Report pregnancies to the Ambrisentan REMS at www.ambrisentanrems.us.com or by calling 1-888-417-3172.
 Report adverse events to FDA by visiting www.fda.gov/medwatch or call 1-800-FDA-1088.

For Ambrisentan REMS information contact:
 Phone: 1-888-417-3172
 Fax: 1-866-750-9802

 Prescribers

The goal of the Ambrisentan Risk Evaluation and Mitigation Strategy (REMS) is to mitigate the risk of embryo-fetal toxicity associated with ambrisentan by:

- Ensuring prescribers are educated on the following:
 - the risks of embryo-fetal toxicity
- Ensuring prescribers are educated on and adhere to the following:
 - counseling patients about these risks and the need for monthly monitoring
 - enrolling patients in the Ambrisentan REMS
 - monitoring patients at baseline and monthly
- Ensuring that pharmacies are educated on the following:
 - the risks of embryo-fetal toxicity
- Ensuring that pharmacies are educated on and adhere to the following:
 - confirming that the appropriate patient monitoring and counseling has occurred before dispensing ambrisentan
- Ensuring that patients are informed about:
 - the risks of embryo-fetal toxicity
 - appropriate baseline and monthly patient monitoring
 - appropriate contraception

Prescriber Requirements

How do I become certified in the Ambrisentan REMS?

- 1 Review the following educational materials to understand the Ambrisentan REMS and the risks of ambrisentan:
 - [Prescribing Information](#)
 - [Prescriber and Pharmacy Guide](#)
- 2 Complete and submit the [Prescriber Enrollment Form](#):
 - Online
 - By fax

How do I enroll my patient in the Ambrisentan REMS and what steps should I take prior to treatment initiation?

- 1 For all females: Assess the female's reproductive status as described in the [Prescriber and Pharmacy Guide](#).
- 2 For all females: Counsel the patient that the drug is only available through a restricted distribution program.
- 3 For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for one month following treatment discontinuation, and the need to use emergency contraception using the [Guide for Female Patients](#).
- 4 For females of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.
- 5 For females of reproductive potential: Prescribe no more than a 30 days' supply.
- 6 For a Pre-Pubertal Female: Counsel the patient and parent/guardian on the risk of embryo-fetal toxicity using the [Guide for Female Patients](#).
- 7 Enroll all female patients by completing the [Patient Enrollment Form](#) prior to prescribing ambrisentan:
 - Online
 - By fax

Once a patient is on ambrisentan, how often should I monitor my patients?

- For a female of reproductive potential: Counsel the patient if she is not complying with the required testing or if she is not using appropriate contraception.
- For a female of reproductive potential: Assess the patient's pregnancy status by ordering and reviewing her pregnancy test result.
- For a Pre-Pubertal Female: Assess the patient's reproductive status regularly.
- For a Pre-Pubertal Female at least age 8 or older: Document reproductive status and submit to the Ambrisentan REMS at least annually using the [Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form](#).
- At all times for all patients, report a change or misclassification in reproductive status to the Ambrisentan REMS using the [Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form](#) within 10 days of being aware of a change.
 - Online
 - By fax
- Notify the Ambrisentan REMS if any patient becomes pregnant during ambrisentan treatment or within one month following treatment discontinuation.

 PDFs for Download

Resources for Prescribers

[Ambrisentan REMS Prescriber and Pharmacy Guide](#)

[Ambrisentan REMS Prescriber Enrollment and Agreement Form](#)

[Ambrisentan REMS Patient Enrollment and Consent Form](#)

[Ambrisentan REMS Guide for Female Patients](#)

[Ambrisentan REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form](#)

Patients

What is Ambrisentan?

Ambrisentan is a prescription medicine used to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Ambrisentan can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

What are the serious risks of Ambrisentan?

Ambrisentan can cause serious birth defects if taken during pregnancy. Females must not be pregnant when they start taking ambrisentan or become pregnant while taking ambrisentan, or for one month after stopping ambrisentan.

How do I become enrolled in the Ambrisentan REMS?

- 1 Read the [Guide for Female Patients](#).
- 2 Review and discuss all information with your doctor.
- 3 Enroll in the Ambrisentan REMS by completing the [Patient Enrollment Form](#) with your doctor.

Please refer to the details provided below and in the [Guide for Female Patients](#) for further clarification on the Ambrisentan REMS requirements.

What are the Ambrisentan REMS requirements for me?

Females Who Cannot Get Pregnant

You are considered a female who **cannot** get pregnant if you have not yet entered puberty, **or** you do not have a uterus, **or** you have gone through menopause, **or** you are infertile for any other medical reason and this infertility is permanent and cannot be reversed.

To receive ambrisentan, you must:

- Talk to your doctor to ensure the benefits outweigh the risks of ambrisentan.
- Review this webpage on the [Guide for Female Patients](#).
- Enroll in the Ambrisentan REMS by completing the [Patient Enrollment Form](#).
- Receive counseling from your prescriber on the risk of serious birth defects (see potential females only).
- Tell your prescriber if you become pregnant or your ability to become pregnant changes.
- If you are over the age of 18, be rechecked every year to see if your ability to become pregnant changes and tell your prescriber if your ability to become pregnant changes.
- If you are the parent or caregiver of a female child who starts taking ambrisentan before reaching puberty, you should check your child regularly to see if she is developing signs of puberty. Tell your doctor right away if you notice that she is developing breast buds or pubic hair. Your doctor should decide if your child has reached puberty. **Your child may reach puberty before having her first menstrual period.**

Females Who Can Get Pregnant

You are considered to be a female who **can** get pregnant if you have entered puberty, have a uterus, and have not gone through menopause.

To receive ambrisentan, you must:

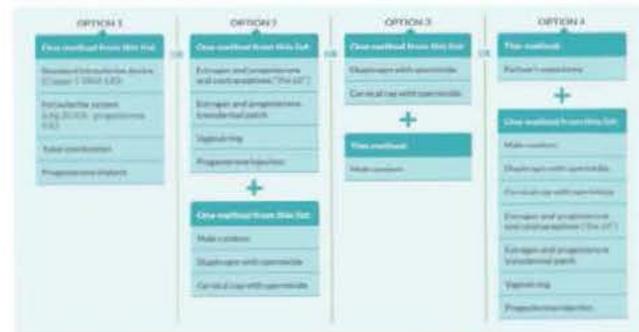
- Talk to your doctor to ensure the benefits outweigh the risks of ambrisentan.
- Review this webpage on the [Guide for Female Patients](#).
- Have a negative pregnancy test before you start taking ambrisentan and before you receive your refills. Your doctor orders the pregnancy test for you.
- Enroll in the Ambrisentan REMS by completing the [Patient Enrollment Form](#).
- Receive counseling from your prescriber on the risk of serious birth defects.
- Be sure to take your monthly pregnancy test as ordered by your doctor. Your certified pharmacy will ask you and ask if you have taken the test before shipping your refill. If you do not take your pregnancy test every month, you may not receive your ambrisentan on time.
- Agree to be contacted by the Ambrisentan REMS if you become pregnant while on ambrisentan or within one month of stopping treatment.

Do not have unprotected sex (intercourse). Use appropriate birth control during your ambrisentan treatment and for one month after stopping your ambrisentan treatment because the medicine may still be in your body.

Talk to your doctor or pharmacist right away if you have unprotected sex, if you think your birth control has failed, or if you think you may be pregnant. Your doctor may tell you to use emergency birth control. Do not wait until your next appointment to tell your doctor if you miss your menstrual period or if you think you may be pregnant.

What are my birth control options?

If you are a female who can get pregnant, your doctor will talk to you about your birth control options. Use the diagram below to help decide what birth control options are best for you. Talk to your doctor if you have questions about your birth control options. Tell your doctor if you want to change your birth control method. You may choose from the four options listed below. More than one birth control method might be needed every time you have sex.



How will I receive my ambrisentan medicine?

Certified pharmacies provide products and services for patients with certain diseases. Only certified pharmacies can provide ambrisentan to you. In some cases, your insurance company may require you to use a specific out-of-network pharmacy.

Your certified pharmacy ships your ambrisentan refill to you. Before each shipment, you will be called to confirm that you have taken a monthly pregnancy test before refilling your prescription. It is important that your certified pharmacy is able to contact you in order to avoid delays in your refills.

If you have questions or concerns about ambrisentan, talk to your doctor. Please call 1-888-417-3172 for more information about the Ambrisentan REMS.

PDFs for Download

Resources for Patients

[Ambrisentan REMS Guide for Female Patients](#)

Rx Outpatient Pharmacies

Only a limited number of certified pharmacies will dispense ambrisentan for outpatients. In order for patients to receive ambrisentan, all outpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the program.

Contact the Ambrisentan REMS to obtain contact information for certified outpatient pharmacies and distributors who are authorized to ship to certified outpatient pharmacies.

To become certified, outpatient pharmacies must:

- 1 Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Ambrisentan REMS on behalf of the pharmacy.
- 2 Review the *Prescriber and Pharmacy Guide*.
- 3 Enroll in the Ambrisentan REMS by completing the *Outpatient Pharmacy Enrollment Form* and submitting it to the Ambrisentan REMS:
 - By fax
- 4 Train all relevant staff involved in dispensing ambrisentan on Ambrisentan REMS procedures and materials using the *Prescriber and Pharmacy Guide*.
- 5 Ensure the pharmacy is able to support electronic data exchanges and communications with the Ambrisentan REMS.
- 6 Establish processes and procedures to verify the patient's prescriber is enrolled for all patients and if the patient is female, verify the patient is enrolled and the reproductive status of the patient has not changed.
- 7 For females of reproductive potential: establish processes and procedures to verify that pregnancy testing is completed or the prescriber authorizes the refill.

To Ensure Compliance with Ambrisentan REMS requirements, outpatient pharmacies must:

- 1 Before dispensing ambrisentan,
 - Obtain authorization to dispense each prescription by contacting the Ambrisentan REMS online or by phone at 1-888-417-3172 to verify that the patient's prescriber is enrolled for all patients and if the patient is female, verify the patient is enrolled and the reproductive status has not changed.
 - For Females of Reproductive Potential:
 - Counsel patient on the risk of embryo-fetal toxicity and the need to use highly reliable contraception and emergency contraception, to get monthly pregnancy tests and to inform the prescriber of a pregnancy immediately.
 - Contact each FRP or their prescriber, every month to verify that the pregnancy testing is complete or the prescriber authorizes the refill.
 - Dispense no more than a 30 days' supply
- 2 At all Times:
 - Report pregnancies to the Ambrisentan REMS.
 - Report a change or misclassification in reproductive status to the Ambrisentan REMS
 - Do not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers
 - Maintain and submit records of daily product dispensing data for female patients to the Ambrisentan REMS
 - Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and being followed.

Login is available for certified pharmacies.

PDFs for Download

Resources for Outpatient Pharmacies

[Ambrisentan REMS Outpatient Pharmacy Enrollment Form](#)

[Ambrisentan REMS Prescriber and Pharmacy Guide](#)



Inpatient Pharmacies

Due to the risk of embryo-fetal toxicity, ambrisentan is available only through a restricted program called the Ambrisentan Risk Evaluation and Mitigation Strategy (REMS). In order for patients to receive ambrisentan, all inpatient pharmacies that wish to stock this product, must enroll in the Ambrisentan REMS and agree to comply with the requirements of the Ambrisentan REMS.

Contact the Ambrisentan REMS to obtain contact information for certified outpatient pharmacies and distributors who are authorized to ship to certified inpatient pharmacies.

To become certified, inpatient pharmacies must:

- 1 Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Ambrisentan REMS on behalf of the pharmacy.
- 2 Have the authorized representative review the *Prescriber and Pharmacy Guide*.
- 3 Enroll in the Ambrisentan REMS by completing the *Inpatient Pharmacy Enrollment Form* and submitting it to the Ambrisentan REMS:
 - Online
 - By fax
- 4 Train all relevant staff involved in dispensing on Ambrisentan REMS procedures and materials using the *Prescriber and Pharmacy Guide*.
- 5 Establish processes and procedures to verify the patient's prescriber is enrolled for all patients and if the patient is female verify the patient is enrolled.
- 6 For females of reproductive potential: establish processes and procedures to verify that the patient has been counseled on the risk of embryo-fetal toxicity, the need to use highly reliable contraception, and emergency contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately.

To Ensure Compliance with Ambrisentan REMS requirements, inpatient pharmacies must:

- 1 Before dispensing ambrisentan:
 - Verify with the Ambrisentan REMS that the patient's prescriber is enrolled for all patients and if the patient is female, verify the patient is enrolled by contacting the Ambrisentan REMS online or by phone at 1-888-417-3172.
 - For females of reproductive potential: Verify that the patient has been counseled on the risk of embryo-fetal toxicity and pregnancy testing is complete.
- 2 Prior to discharge of a Patient:
 - Dispense no more than a 15 days' supply upon discharge.
- 3 At all Times:
 - Report pregnancies to the Ambrisentan REMS.
 - Report a change or misclassification in reproductive status to the Ambrisentan REMS.
 - Do not distribute, transfer, loan, or sell ambrisentan, except to certified dispensers.
 - Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and being followed.

Login is available for certified pharmacies.



PDFs for Download

Resources for Inpatient Pharmacies

[Ambrisentan REMS Inpatient Pharmacy Enrollment Form](#)

[Ambrisentan REMS Prescriber and Pharmacy Guide](#)

Contact us

Phone

1-888-417-3172

Fax

1-866-750-9802

Hours of Operation

Monday - Friday
8:00 AM - 8:00 PM ET

Report pregnancies to the Ambrisentan REMS at www.ambrisentanrems.us.com or by calling 1-888-417-3172.
Report adverse events to FDA by visiting www.fda.gov/medwatch or call 1-800-FDA-1088.

For Ambrisentan REMS information contact:
Phone: 1-888-417-3172
Fax: 1-866-750-9802

Reference ID: 4411238

[Privacy Policy](#) [Terms of Use](#) [Contact us](#)

ARC008_ApprovalYYYYMMM_V#.#

Resources

Resources for Prescribers

- [Ambrisentan REMS Prescriber and Pharmacy Guide](#)
- [Ambrisentan REMS Prescriber Enrollment and Agreement Form](#)
- [Ambrisentan REMS Patient Enrollment and Consent Form](#)
- [Ambrisentan REMS Guide for Female Patients](#)
- [Ambrisentan REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form](#)

Resources for Female Patients

- [Ambrisentan REMS Guide for Female Patients](#)

Resources for Outpatient Pharmacies

- [Ambrisentan REMS Outpatient Pharmacy Enrollment Form](#)
- [Ambrisentan REMS Prescriber and Pharmacy Guide](#)

Resources for Inpatient Pharmacies

- [Ambrisentan REMS Inpatient Pharmacy Enrollment Form](#)
- [Ambrisentan REMS Prescriber and Pharmacy Guide](#)

Login

Access to the application is limited to certified prescribers and pharmacies. If you have not received a user name, please contact the Ambrisentan REMS at 1-888-417-3172.

Login

Please enter your User Name

LOGIN

[Forgot User Name](#)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY R SOUTHWORTH
03/28/2019 03:26:30 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022081Orig1s039

OTHER REVIEW(S)

Internal Consults

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan E. Blair, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Puja Shah, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP
Alycia Anderson, Safety Regulatory Project Manager, OSE
Laura Zendel, Acting Team Leader, DRISK
Jacqueline Sheppard, Risk Management Analyst, DRISK
Doris Auth, Associate Director, DRISK
Carole Broadnax, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: September 28, 2018

Re: NDA 22081
ANDAs 20852; 208354; 209509
Ambrisentan REMS Consortium (ARC) Shared System REMS
Comments on draft Risk Evaluation and Mitigation Strategies (REMS)
Materials (Submission date: August 30, 2018)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for ambrisentan:

- Healthcare Provider (HCP) REMS Materials:
 - Ambrisentan REMS Prescriber Enrollment and Agreement Form
 - Ambrisentan REMS Outpatient Pharmacy Enrollment Form
 - Ambrisentan REMS Inpatient Pharmacy Enrollment Form
 - Ambrisentan REMS Prescriber and Pharmacy Guide
 - Ambrisentan REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form

- Direct-to-Consumer (Patient) REMS Materials:
 - Ambrisentan REMS Guide for Female Patients
 - Ambrisentan REMS Patient Enrollment and Consent Form

- Ambrisentan REMS Website (www.ambrisentanrems.us.com)

The version of the draft REMS materials used in this review were sent from DRISK (Joan E. Blair) via email on August 30, 2018. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for ambrisentan.

General Comment

Please remind the Ambrisentan REMS Consortium (ARC) comprised of Gilead Pharmaceuticals, Watson Laboratories, SigmaPharm Laboratories, Par Pharmaceuticals, (b) (4), Sun Pharmaceuticals, and Mylan Pharmaceuticals, that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Ambrisentan REMS Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- Ambrisentan REMS Guide for Female Patients
- Ambrisentan REMS Website (www.ambrisentanrems.us.com)

○ **Indications/Use**

- These REMS pieces include the following presentation regarding the indication for ambrisentan.

“Ambrisentan is a prescription medicine used to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Ambrisentan can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.”

These presentations fail to include important information regarding the indication for ambrisentan. Specifically, the “What is Letairis?” section of the Letairis Medication Guide (MG) states (in pertinent part):

- “When taken with tadalafil, Letairis is used to reduce the risk of your disease progressing, to reduce the risk of hospitalization due to worsening pulmonary arterial hypertension (PAH), and to improve your ability to exercise.
- It is not known if Letairis is safe and effective in children.”

We recommend revising these REMS pieces to include this important information.

- Ambrisentan REMS Guide for Female Patients
- Ambrisentan REMS Website (www.ambrisentanrems.us.com)
- Ambrisentan REMS Patient Enrollment and Consent Form

○ **Indications/Use**

- We note that these REMS pieces include instructions to annually monitor patients over the age of eight for changes in reproductive status. Considering that these REMS pieces will be communicated directly to the consumer (patient), we are concerned that this instruction may misleadingly imply that ambrisentan has been

studied and approved in children eight years of age and older, when this is not the case. Section 8.4 of the Letairis Prescribing Information (PI) states that the, "Safety and effectiveness of Letairis in pediatric patients have not been established." This misleading implication is further exacerbated by the inadequate communication of the indication described above for the Ambrisentan REMS Guide for Female Patients and Ambrisentan REMS Website. Therefore, we recommend deleting instructions for annual monitoring of changes in reproductive status in patients over the age of eight from these direct-to-consumer (patient) REMS pieces.

- Ambrisentan REMS Prescriber and Pharmacy Guide
 - **Indications/Use**
 - Page three of this REMS piece partially presents the indication for ambrisentan. The INDICATIONS AND USAGE section of the Letairis PI also includes an indication of, "In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability." We recommend revising this REMS piece to include this information.
 - Ambrisentan REMS Patient Enrollment and Consent Form
 - Ambrisentan REMS Pharmacy Inpatient Enrollment Form
 - Ambrisentan REMS Pharmacy Outpatient Enrollment Form
 - Ambrisentan REMS Prescriber Enrollment and Agreement Form
 - Ambrisentan REMS Website (www.ambrisentanrems.us.com)
 - Ambrisentan REMS Prescriber and Pharmacy Guide
 - **Risk**
 - These REMS pieces convey the importance of using "reliable contraception" to prevent pregnancy in Females of Reproductive Potential (FRP) during treatment with ambrisentan and for one month following treatment discontinuation. The use of "reliable contraception" is a vague descriptor as estrogen and progesterone oral contraceptives ("the pill") are often associated as being a highly reliable form of contraception. However, under the Ambrisentan REMS Program, FRP who use "the pill" for contraception would also require an additional form of contraception as a REMS requirement. According to section 8.6 of the Letairis PI (underlined emphasis added):

"Patients may choose one highly effective form of contraception (intrauterine devices (IUD), contraceptive implants or tubal

sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods)"

Furthermore, the Letairis Medication Guide states (bolded emphasis original; underlined emphasis added):

"Females who are able to get pregnant must use two acceptable forms of birth control during treatment with Letairis..."

Therefore, these REMS pieces minimize the importance of using appropriate or acceptable contraceptive methods under the Ambrisentan REMS Program. We recommend revising these presentations to avoid this misleading impression.

- Ambrisentan REMS Pharmacy Inpatient Enrollment Form
- Ambrisentan REMS Pharmacy Outpatient Enrollment Form
- Ambrisentan REMS Website (www.ambrisentanrems.us.com)
- Ambrisentan REMS Prescriber and Pharmacy Guide

- **Risk**

- These REMS pieces include limited information regarding counseling points for Inpatient and Outpatient Pharmacists. For example, the Ambrisentan REMS Website includes the following presentations (bolded emphasis original; underlined emphasis added):

- **"OUTPATIENT PHARMACY CONTENT**

...

For females of reproductive potential:

- **Counsel** patient on the risk of embryo-fetal toxicity and the need to use highly reliable contraception and emergency contraception, to get monthly pregnancy tests, and to inform the prescriber of a pregnancy immediately."

- **"INPATIENT PHARMACY CONTENT**

...

For females of reproductive potential: Verify that the patient has been counseled on the risk of embryo-fetal toxicity and pregnancy testing is complete."

These and similar presentations within the REMS pieces mentioned above omit REMS related risk information and minimize the importance of the role of a Pharmacist in the Ambrisentan REMS

Program. Specifically, section 8.6 of the Letairis PI states (emphasis added):

- “Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and 1 month after stopping treatment with Letairis.”
- “Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. . . . Counsel patients on pregnancy planning and prevention, including emergency contraception, . . .”

We recommend revising the counseling points for Inpatient and Outpatient Pharmacists mentioned above to include this important REMS related risk information. For example, we note that the Ambrisentan REMS Prescriber Enrollment and Agreement Form includes a concise presentation of the important counseling points regarding the REMS related risk of embryo-fetal toxicity, “For females of reproductive potential, I will counsel the patient about the risk of embryo-fetal toxicity, the need to use highly reliable contraception during treatment and for 1 month following treatment discontinuation; and the need to use emergency contraception.”

- Ambrisentan REMS Website (www.ambrisentanrems.us.com)
- Ambrisentan REMS Prescriber and Pharmacy Guide

- **Risk**

- These REMS pieces include the following instruction (emphasis added):
 - “Ensuring prescribers are educated on and adhere to the following:
 - Counseling patients about these risks and the need for monthly monitoring”

These claims within the REMS pieces listed above use the phrase “these risks” to communicate the Boxed Warning of embryo-fetal toxicity, thereby dissociating the REMS related risk of embryo-fetal toxicity from ambrisentan specifically (emphasis added). We recommend revising these REMS pieces to specify the REMS related risk of embryo-fetal toxicity associated with the use of ambrisentan.

- Ambrisentan REMS Website (www.ambrisentanrems.us.com)

- **Risk**

- Page two of the Ambrisentan REMS Website includes the following information for “**Female Patients**” (bolded emphasis original; underlined emphasis added):

“2. Receive counseling from your prescriber to understand the risks associated with ambrisentan

This claim is vague and fails to specify the REMS related risk of embryo-fetal toxicity, thus minimizing this important risk concept. We recommend specifying the REMS related risk associated with ambrisentan in consumer-friendly language (e.g., “to understand the risk of serious birth defects associated with ambrisentan”).

- Additionally, page two includes information regarding the importance of appropriate birth control and pregnancy tests during treatment with ambrisentan and for one month after treatment discontinuation. However, page two of the Ambrisentan REMS Website fails to communicate any information regarding the importance of emergency contraception, as outlined in section 8.6 of the Letairis PI. Therefore, we recommend revising this REMS piece to include this important information.

- **Communication Suggestion**

- We note that page two includes the acronym “FRP” that has not been previously defined. We suggest defining acronyms with their initial use.
- Page (b)(4) includes the following instruction for Females Who Cannot Get Pregnant (emphasis added):

- "Receive counseling from your prescriber on the risk of serious birth defects (b)(4) only)"

To be consistent with the definitions of "Females Who Cannot Get Pregnant" and for ease of understanding, we suggest revising this presentation to specify that counseling is required for females who have not yet entered puberty (i.e., pre-pubertal).

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PUJA J SHAH
09/28/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Reviewer Name Jacqueline Sheppard, PharmD
Health Communications Analyst Joan Blair, RN, MPH
Team Leader Laura Zendel, PharmD
Deputy Division Director Jamie Wilkins, PharmD
Review Completion Date March 21, 2019
Subject Evaluation of proposed shared REMS for
 ambrisentan
Established Name Ambrisentan
OND Review Division Division of Cardiovascular and Renal Products
Therapeutic Class Endothelin Receptor Antagonist
Dosage Form 5 mg and 10 mg tablets for oral administration

| Application Type/Number | Sponsor | OSE- RCM |
|-------------------------|-------------------------|-----------|
| NDA 022081 S-039 | Gilead Pharmaceuticals | 2015-1623 |
| ANDA 208354 | SigmaPharm Laboratories | 2018-1963 |
| ANDA 208252 | Watson Pharmaceuticals | 2018-1962 |
| ANDA 209509 | Par Pharmaceuticals | 2018-1961 |
| (b) (4) | | |
| ANDA 210784 | Sun Pharmaceuticals | 2018-1505 |
| ANDA 208441 | Mylan Pharmaceuticals | 2019-602 |

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the proposed single, shared system (SSS) risk evaluation and mitigation strategy (REMS) submitted March 15, 2019 for ambrisentan from Gilead Pharmaceuticals, Watson Laboratories, SigmaPharm Laboratories, Par Pharmaceuticals, (b) (4) (b) (4) Sun Pharmaceuticals, and Mylan Pharmaceuticals herein referred to in this review as the Ambrisentan REMS Consortium (ARC) in response to the February 25, 2019 DRISK review.

The ARC proposes minor changes to the REMS Document and appended materials to reflect the operations of the REMS program. The Agency agrees with the proposed changes to the REMS document and appended materials and finds them acceptable. The SSS REMS consists of elements to assure safe use (ETASU), implementation system, and a timetable for submission of assessments and will go into effect on the date of the full approval of the first abbreviated New Drug Application (ANDA) referencing NDA 022081 replacing the approved Letairis REMS at that time.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed single, shared system (SSS) risk evaluation and mitigation strategy (REMS) submitted March 15, 2019 for ambrisentan from Gilead Pharmaceuticals, Watson Laboratories, SigmaPharm Laboratories, Par Pharmaceuticals, (b) (4) (b) (4) Sun Pharmaceuticals, and Mylan Pharmaceuticals herein referred to in this review as the Ambrisentan REMS Consortium (ARC) in response to the February 25, 2019 DRISK review. The SSS REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments and will go into effect on the date of the full approval of the first abbreviated New Drug Application (ANDA) referencing NDA 022081 replacing the approved Letairis REMS at that time.

2 Background

2.1 REGULATORY HISTORY

The following is a summary of the regulatory history for the proposed SSS REMS relevant to this review:

- **02/25/19:** The Agency provided comments¹ on the REMS document and appended materials.
- **03/07/2019:** The ARC sent an e-mail submission of the REMS documents and appended materials. A formatted website is not included in the e-mailed submission.
- **03/15/19:** The Agency sent communication to the ARC via e-mail providing the most updated version of the assessment plan as the assessment plan attached to the supporting document was outdated.
- **03/15/19:** The Agency received REMS Amendments from the ARC.

3 Results of the Review of the ARC's Proposed REMS

The ARC incorporated and responded appropriately to all of the Agency's comments and revisions requested in the February 25, 2019 DRISK Review with exceptions detailed below.

3.1 REMS DOCUMENT

The ARC proposes to revise the audit statement in the REMS document to include audits of all certified outpatient pharmacies and risk-based auditing of inpatient pharmacies.

DRISK Response: The Agency agrees with this proposal. The risk based auditing plan of inpatient pharmacies is outlined in the supporting document and the statement revision in the REMS document reflects the operations of the program.

3.2 APPENDED MATERIALS

3.2.1 Outpatient Pharmacy Enrollment Form

The ARC proposes to maintain attestations about electronic communications and submissions of REMS materials in the Outpatient Pharmacy Enrollment Forms.

DRISK Response: The Agency agrees with the changes to the Outpatient Pharmacy Enrollment Form. The proposed changes reflect the operations of the program.

3.2.2 Website

The ARC proposes to add a dialogue box to the homepage of the Ambrisentan REMS website. This dialogue box will appear if the stakeholder is routed to the Ambrisentan REMS website from the Letairis REMS website.

DRISK Response: The Agency agrees with the addition of the dialogue box.

3.3 REMS SUPPORTING DOCUMENT AND ASSESSMENT PLAN

An updated version of the Assessment Plan was provided to the ARC on March 15, 2019 and this version will be attached to the approval letter. The updated Assessment Plan may be submitted as a REMS correspondence at a later date.

4 Conclusion and Recommendations

DRISK finds the proposed ambrisentan SSS REMS document, appended materials, and REMS supporting document as submitted on March 15, 2019 acceptable. The SSS REMS will replace the previously approved Letairis REMS at the time of approval.

5 Appendices

5.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

1. Gilead Pharmaceuticals. Proposed REMS for ambrisentan. NDA 022081 -S039, dated 3/15/19
2. SigmaPharm Laboratories, Proposed REMS for ambrisentan. NDA 208354, dated 3/15/19
3. Watson Pharmaceuticals. Proposed REMS for ambrisentan. ANDA 208252, dated 3/15/19
4. Par Pharmaceuticals. Proposed REMS for ambrisentan. ANDA 209509, dated 3/15/19
5. (b) (4)
6. Sun Pharmaceuticals. Proposed REMS for ambrisentan. ANDA 210784, dated 3/15/19
7. Mylan Pharmaceuticals. Proposed REMS for ambrisentan. ANDA 208441, dated 3/15/19
8. Sheppard J, Blair J. DRISK. REMS Review for Ambrisentan SSS, dated 2/25/19
9. Gilead. Letairis REMS. NDA 022081 approved on 05/29/09 and last modified on 11/30/18.

5.2 APPENDED MATERIALS

REMS Document

Prescriber and Pharmacy Guide

Prescriber Enrollment Form

Patient Enrollment Form

Guide for Female Patients

Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form

Outpatient Pharmacy Enrollment Form

Inpatient Pharmacy Enrollment Form

REMS Program Website

¹Sheppard J, Blair J. DRISK. REMS Review for Ambrisentan SSS, dated February 25, 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JACQUELINE E SHEPPARD
03/21/2019 04:21:53 PM

LAURA A ZENDEL
03/21/2019 04:23:45 PM

JAMIE C WILKINS PARKER
03/21/2019 04:27:53 PM

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Reviewer Name Jacqueline Sheppard, PharmD
Health Communications Analyst Joan Blair, RN, MPH
Team Leader Laura Zendel, PharmD
Deputy Division Director Jamie Wilkins, PharmD
Review Completion Date February 25, 2019
Subject Evaluation of proposed Ambrisentan shared system REMS
Established Name Ambrisentan
OND Review Division Division of Cardiovascular and Renal Products
Therapeutic Class Endothelin Receptor Antagonist
Dosage Form 5 mg and 10 mg tablets for oral administration

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| | | (b) (4) |
| ANDA 210784 | Sun Pharmaceuticals | 2018-1505 |
| ANDA 208441 | Mylan Pharmaceuticals | 2018-1964 |

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the proposed shared system (SS) risk evaluation and mitigation strategy (REMS) amendments submitted September 13, 2018 and October 12, 2018 for ambrisentan from Gilead Pharmaceuticals, Watson Laboratories, SigmaPharm Laboratories, Par Pharmaceuticals, (b) (4), Sun Pharmaceuticals, and Mylan Pharmaceuticals herein referred to in this review as the Ambrisentan REMS Consortium (ARC) in response to the August 10, 2018 DRISK review and September 28, 2018 Agency communication.

The ARC responded appropriately to the Agency's requests, however Agency thinking has changed concerning adverse event reporting requirements in REMS. As the purpose of a REMS is to focus on the determined risk(s) mitigated by the program, the reporting of all adverse events associated with the drug is no longer required for this REMS. As such, the REMS is being revised to remove the reporting on non-REMS related risks.

Therefore, additional revisions are required to the proposed SS REMS document, appended materials, and supporting document to be acceptable.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed Ambrisentan shared system (SS) risk evaluation and mitigation strategy (REMS) amendments submitted by the Ambrisentan REMS Consortium (ARC) comprised of Gilead Pharmaceuticals, Letairis, new drug application (NDA) 022081 and the following abbreviated new drug applications (ANDAs): Watson (ANDA 208252), SigmaPharm (ANDA 208354), Par (ANDA 209509), (b) (4) Sun (ANDA 210784), and Mylan Pharmaceuticals (ANDA 208441) on September 13, 2018 and October 12, 2018 in response to the August 10, 2018 DRISK Review and September 28, 2018 Agency communication.

2 Background

2.1 REGULATORY HISTORY

The following is a summary of the regulatory history for the proposed SS REMS relevant to this review:

- **08/10/18:** The Agency provides comments to the ARC addressing the revised REMS document, creation of a combined Prescriber and Pharmacy Guide, and retitling of the Guide Females who Can Get Pregnant to Guide for Female Patients.
- **09/13/18:** The ARC submits a REMS amendment in response to the August 10, 2018 Agency comments.
- **09/28/18:** The Agency provides comments to the ARC addressing the proposed website screenshots. The Agency requests the ARC make schematic changes to the public facing screenshots as well as provide screenshots showing the functionality of the website behind the prescriber and pharmacy login pages.
- **10/12/18:** The ARC submits website screenshots addressing the schematic changes requested in the Agency September 28, 2018 communication including proprietary non-public screenshots for Agency review.

- **10/24/18:** The Agency sends an information request (IR) via email requesting a copy of the proposed outreach plan for each stakeholder detailing the transition from the Letairis REMS to the ambrisentan shared system REMS.
- **11/16/18:** The ARC provides an outreach plan through a REMS correspondence in response to Agency request. The proposed outreach plan including targeted letters to affected stakeholders.

3 Results of the Review of the ARC's Proposed REMS

The ARC submitted REMS amendments on September 13, 2018 and October 12, 2018 in response to the Agency's comments on August 10, 2018 and September 28, 2018 to 1) retitle the *Guide for Females who can Get Pregnant* and revise the content to include information applicable to all female patients 2) retitle the *Prescriber Guide* for the Ambrisentan REMS Program and revise the content to include information for inpatient and outpatient pharmacies and 3) revise the website to include schematic changes for end user clarity.

The proposed REMS document, appended materials, and supporting document require additional revisions to be acceptable.

3.1 REMS DOCUMENT

The ARC submits an updated REMS document based upon the Agency comments.

Reviewer Comments: *The Agency proposes additional changes to the REMS document. Please see comments in Section 4.*

3.2 REMS MATERIALS

The ARC proposes updates to the following REMS materials in response to the Agency's comments:

- *Guide for Female Patients*
- *Prescriber and Pharmacy Guide*
- Website

Reviewer Comments: *These documents require additional changes. Please see comments in Section 4.*

3.3 SUPPORTING DOCUMENT

3.3.1 Outreach Plan

The ARC submits an Outreach Plan consisting of targeted letters in response to the Agency's comments.

Reviewer Comments: *These materials require additional changes. Please see comments in Section 4.*

4 Discussion

The ARC responded appropriately to the Agency's comments on the REMS document and submitted an updated bifurcated REMS document. However, Agency thinking has changed concerning the reporting of adverse events in REMS programs since the time of approval of the Letairis REMS. As a REMS focuses on the risk(s) to be mitigated by the program, the reporting of all adverse events associated with the

drug is no longer required for this program. The Agency will provide an updated REMS document to the ARC, and is attached to this review.

The ARC submitted an updated *Guide for Female Patients* in response to the Agency's comments. The updated guide adds information for patients of non-reproductive potential to the previously existing *Guide for Women who Can Get Pregnant*. While the ARC adequately addresses the Agency's comments, the updated document requires further revision to correct minor grammatical errors.

The ARC submitted an updated *Prescriber and Pharmacy Guide* in response to the Agency's comments to add information for pharmacies and pharmacists to the existing *Prescriber Guide*. The information was added appropriately, however, the *Prescriber and Pharmacy Guide* needs to be updated remove the adverse events reporting information.

The ARC proposes to modify the Statement of Medical Necessity Chart on the *Patient Enrollment and Consent Form* to include ICD (International Classification of Disease) codes based on stakeholder feedback. The Agency agrees with this proposal.

The ARC also submitted an updated website in response to the Agency's comments. However, there are minor edits needed to align the forward facing Ambrisentan REMS website with the current REMS document and to increase readability. Additionally, in response to Agency request, the ARC submitted additional non-public facing proprietary website screenshots. These non-public facing websites also need to be modified to align with changes to the REMS document and should be appended to the supporting document.

The ARC proposes an outreach plan in response to the October 24, 2018 Agency IR. The outreach plan is comprised of targeted letters to each stakeholder (Healthcare Provider, Inpatient Pharmacy, Outpatient Pharmacy, Wholesaler) detailing the transition from the Letairis REMS to the ambrisentan shared system REMS. The letters need to be revised to align with the requirements in the REMS document, edited for increased readability, and should include information so prescribers and pharmacists are able to determine which products are available through the Ambrisentan REMS program.

In conjunction with DRISK's review of the Appended Materials, the Office of Prescription Drug Promotion (OPDP) was consulted on February 16, 2018. We consider OPDP's recommendations and note their concerns.

OPDP expressed concern with the *Guide for Female Patients*, *Patient Enrollment and Consent Form*, and the REMS Website. These materials include instructions to annually monitor patients over the age of eight for changes in reproductive status. OPDP is concerned that this instruction may misleadingly imply that ambrisentan has been studied and approved in children eight years of age and recommends deleting instructions for annual monitoring of changes in reproductive status in patients over the age of eight from patient directed materials. However, we disagree as the Prescribing Information and the ambrisentan materials do not specify an age limitation of use. There is a possibility that ambrisentan will be used in pre-pubertal females, even though safety and efficacy of ambrisentan has not been established for this patient population. Therefore, including information on annual monitoring of changes in reproductive status in patients over the age of eight is warranted as is included in the currently approved Letairis REMS.

Additionally, OPDP expressed concerns with the education and counseling points presented in the *Patient Enrollment and Consent Form, Pharmacy Inpatient Enrollment Form, Pharmacy Outpatient Enrollment Form, Prescriber Enrollment and Agreement Form, Website, and Prescriber and Pharmacy Guide*. These REMS pieces convey the importance of using "reliable contraception" to prevent pregnancy in Females of Reproductive Potential (FRP) during treatment with ambrisentan and for one month following treatment discontinuation. OPDP is concerned that the materials minimize the importance of using appropriate or acceptable contraceptive methods under the Ambrisentan REMS Program and recommend revising these presentations to avoid this misleading impression. However, we disagree with this assertion as detailed information is provided to patients on appropriate contraceptive options.

OPDP has concerns that the *Pharmacy Inpatient Enrollment Form, Pharmacy Outpatient Enrollment Form, Website, and Prescriber and Pharmacy Guide* has limited information regarding counseling points for inpatient and outpatient pharmacists and minimizes the importance of the role of a pharmacist in the Ambrisentan REMS Program. OPDP recommends revising the counseling points for inpatient and outpatient pharmacists to include this important REMS related risk information. However, the pharmacist's role in the ambrisentan REMS Program is to ensure that safe use conditions are met prior to dispensing. The task of counseling patients on pregnancy planning and prevention - including emergency contraception options resides with the certified prescriber.

OPDP has concerns that the *Website and Prescriber and Pharmacy Guide* dissociates the REMS related risk of embryo-fetal toxicity from ambrisentan by the use of the phrase "counseling patient about these risks." OPDP recommends revising the materials to state the risk of embryo-fetal toxicity is associated with the the use of ambrisentan. However, we disagree because the risk of embryo-fetal toxicity from ambrisentan is more fully explained in the "Educate and Counsel" section of the *Prescriber and Pharmacy Guide* and in the "What are the serious risk of ambrisentan?" of the *Guide for Female Patients*. Additionally, both the *Prescriber and Pharmacy Guide* and the *Guide for Female Patients* is available on website.

Finally, OPDP has concerns that the website fails to communicate any information regarding the importance of emergency contraception and recommends revising the website to include the missing information. We do not agree with this comment because the website is not designed to include all pertinent information. However, the *Guide for Female Patients*, which is available on the website, does includes information about "emergency birth control" in case of potential pregnancy. We discussed our conclusions with OPDP via email^a and they expressed understanding with our rationale.

Finally, DRISK agrees with all other previously mentioned changes, additions, and deletions made to the REMS Document, appended materials, and supporting document unless otherwise noted.

^a Email exchange between J. Blair (DRISK) and P. Shah (OPDP) dated November 2, 2018

5 Conclusion and Recommendations

The proposed REMS requires further changes to be acceptable.

Comments for the ARC are provided in Section 6.

6 Comments to the ARC

The following comments and attached red-lined REMS document and appended materials are based on the Agency's review of the proposed ambrisentan shared system REMS submitted to NDA 022081 and ANDAs 208354, 280252, 209509, (b) (4) 210784, and 208441. In order to facilitate further review, we ask that you respond to these comments within 10 business days.

A. General Comments

1. We are providing an updated REMS document. Align all materials with the revised REMS document. Please see attached redlined materials.
2. The instruction to report all adverse events to the REMS should be removed from all materials. Agency thinking has changed concerning adverse event reporting requirement in REMS. As the purpose of a REMS is to focus on the determined risk(s) mitigated by the program, the reporting of all adverse events associated with the drug is no longer required for this REMS. As such, the REMS has been revised to remove the reporting on non-REMS related risks.

B. Appended Materials

1. Guide for Female Patients
Revise grammatical errors. Please see attached redlined materials.
2. Website
Align both the public REMS website screenshots and the non-public facing proprietary website with the revised REMS document. Additionally, the non-public website screenshots should be appended to the supporting document.
3. Outreach Plan Letters (Dear Healthcare Provider, Dear Inpatient Pharmacy, Dear Outpatient Pharmacy, Dear Wholesaler)
Update the letters for readability, to include information for stakeholders to determine which products are available through the Ambrisentan REMS program and to align with the REMS document. Additionally, the letters should be appended to the supporting document. Please see attached redlined materials.

7 Appendices

7.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

1. Gilead Pharmaceuticals. Proposed REMS for ambrisentan. NDA 022081 S-039, dated 4/24/18 , 9/28/18, 10/12/18, 11/16/18
2. SigmaPharm. Proposed REMS for ambrisentan. ANDA 208354 , dated 4/24/18, 9/13/18, 10/12/18, 11/16/18
3. Watson. Proposed REMS for ambrisentan. ANDA 208252 , dated 4/24/18, 9/13/18, 10/12/18, 11/16/18
4. Par. Proposed REMS for ambrisentan. ANDA 209509, dated 4/24/18, 9/13/18, 10/12/18, 11/16/18
5.  (b) (4)
6. Sun. Proposed REMS for ambrisentan. ANDA 210784, dated 7/6/18, 9/12/18, 10/12/18, 11/16/18
7. Mylan. Proposed REMS for ambrisentan. ANDA 208441, dated 10/12/18, 11/16/18
8. Gilead. Letairis REMS. NDA 022082 approved on 10/29/09 and last modified on 09/27/17.
9. Sheppard J, Blair J. DRISK. REMS Review for Ambrisentan SS REMS, dated April 3, 2018.

10. Sheppard J, Blair J. DRISK. REMS Review for Ambrisentan SS REMS, dated August 10, 2018.

7.2 APPENDED MATERIALS

Ambrisentan REMS Document

Prescriber and Pharmacy Guide

Prescriber Enrollment and Agreement Form

Patient Enrollment and Consent Form

Guide for Female Patients

Outpatient Pharmacy Enrollment Form

Inpatient Pharmacy Enrollment Form

REMS Website

Dear Healthcare Provider Letter

Dear Inpatient Pharmacy Letter

Dear Outpatient Pharmacy Letter

Dear Wholesaler Letter

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/s/

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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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|--------------------------------------|---|-------------|
| Applicant/Application Numbers | Gilead Pharmaceuticals | NDA 022081 |
| | SigmaPharm Laboratories | ANDA 208354 |
| | Watson Laboratories | ANDA 208252 |
| | Par Pharmaceutical | ANDA 209509 |
| | (b) (4) | (b) (4) |
| | Sun Pharmaceuticals | ANDA 210784 |
| | Mylan Pharmaceuticals | ANDA 208441 |
| OSE RCM # | (b) (4) | |
| Reviewer Name | Jacqueline Sheppard, PharmD | |
| Health Communications Analyst | Joan Blair, RN, MPH | |
| Team Leader | Laura Zendel, PharmD | |
| Deputy Division Director | Jamie Wilkins, PharmD | |
| Review Completion Date | August 10, 2018 | |
| Subject | Evaluation of proposed Ambrisentan shared system REMS | |
| Established Name | Ambrisentan | |
| OND Review Division | Division of Cardiovascular and Renal Products | |
| Therapeutic Class | Endothelin Receptor Antagonist | |
| Dosage Form | 5 mg and 10 mg tablets for oral administration | |

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the proposed Ambrisentan shared system (SS) risk evaluation and mitigation strategy (REMS) submitted by the Ambrisentan REMS Consortium (ARC) comprised of Gilead Pharmaceuticals^a, Watson Laboratories^b, SigmaPharm Laboratories^c, Par Pharmaceuticals^d, [REDACTED]^{(b) (4)}, Sun Pharmaceuticals^f, and Mylan Pharmaceuticals^g on April 24, 2018 in response to the April 4, 2018 DRISK Review¹.

The ARC submitted the April 24, 2018 REMS amendment to: 1) remove the Medication Guide as an element of the REMS and 2) create separate inpatient and outpatient pharmacy enrollment forms. These changes are consistent with the Agency's comments, however, further revisions are required to these forms.

The ARC also accepted all the Agency's provided comments on the REMS document based upon the Agency - provided REMS document. However, the Agency recommends additional changes to the REMS document and appended materials.

Finally, the ARC has not provided a proposed website that shows full functionality of the program. Working screenshots showing both format and content must be provided to the Agency for review.

As such, additional revisions are required to the proposed SS REMS document, appended materials, and supporting document to be acceptable.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed Ambrisentan shared system (SS) risk evaluation and mitigation strategy (REMS) submitted by the Ambrisentan REMS Consortium (ARC) comprised of Gilead Pharmaceuticals, Letairis, new drug application (NDA) 022081 and the following abbreviated new drug applications (ANDAs): Watson (ANDA 208252), SigmaPharm (ANDA 208354), Par (ANDA 209509), [REDACTED]^{(b) (4)} Sun (ANDA 210784), and Mylan Pharmaceuticals (ANDA 208441) on April 24, 2018 in response to the April 4, 2018 DRISK Review.

2 Background

^a Submitted December 5, 2017 (RLD), April 24, 2018

^b Submitted December 1, 2017, April 24, 2018

^c Submitted December 5, 2017, April 24, 2018

^d Submitted December 5, 2017, April 24, 2018

^e REMS not yet submitted

^f REMS not yet submitted

^g REMS not yet submitted

2.1 PRODUCT INFORMATION

Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. It is currently available in 5 mg and 10 mg tablets for oral administration and is dosed at 5 mg once daily, with or without tadalafil 20 mg once daily. At four week intervals, either the dose of Letairis or tadalafil can be increased to Letairis 10 mg or tadalafil 40 mg.

The RLD, Letairis was originally approved on June 15, 2007 under 21 CFR 314.520 Subpart H approval with a Risk Minimization Action Plan (RiskMAP) due to teratogenicity and hepatotoxicity. Letairis was deemed to have a REMS in effect^h because the product had a RiskMAP with restrictive elements. The REMS for Letairis was subsequently approved on October 29, 2009 and was last modified on September 27, 2017. The most recently approved REMS for Letairis consists of a MG, ETASU, an implementation plan, and a timetable for submission of assessments. The goals of the currently approved REMS are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Letairis.
2. To minimize the risk of fetal exposures and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Letairis
 - a. Females who are pregnant must not be prescribed Letairis
 - b. Females taking Letairis must not become pregnant

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for the proposed SS REMS relevant to this review:

- 04/04/18: The Agency provided comments to the ARC addressing the removal of the Medication Guide as an element of the REMS and the creation of separate inpatient and outpatient pharmacy enrollment forms.
- 04/24/18: The ARC submitted a REMS amendment in response to the April 4, 2018 Agency comments to remove the Medication Guide as an element of the REMS and to create separate inpatient and outpatient pharmacy enrollment forms.

3 Results of the Review of the ARC's Proposed REMS

The ARC submitted a REMS amendment in response to the Agency's comments on April 4, 2018 to 1) remove the Medication Guide as an element of the REMS and 2) create separate inpatient and outpatient pharmacy enrollment forms.

However, the proposed REMS document, appended materials, and supporting document require additional revisions to be acceptable.

^h Section 909 of FDAAA provides that drugs approved with restrictive elements before FDAAA was enacted were deemed to have REMS. Sponsors of these products were required to submit proposed REMS by September 21, 2008.

3.1 REMS DOCUMENT

The ARC has created a REMS document based upon the Agency comments.

Reviewer Comments: The Agency has proposed additional changes to the REMS document. Please see comments in Section 4.

3.2 REMS MATERIALS

3.2.1 Inpatient Pharmacy Enrollment Form/ Outpatient Pharmacy Enrollment Form

The ARC has included separate inpatient and outpatient pharmacy enrollment forms in response to the the Agency's comments.

Reviewer Comments: These forms require additional changes. Please see comments in Section 4.

3.2.2 Guide for Females Who Can Get Pregnant/Prescriber Guide for the Ambrisentan REMS Program

Reviewer Comments: The Agency has retitled these forms. Please see comments in Section 4.

4 Discussion

The ARC accepted all the Agency's comments on the REMS document. The Agency has proposed additional changes to the REMS document in order to 1) provide further clarity on the program requirements and operations 2) remove all references to the Medication Guide and 3) retitle names of Appended Materials when appropriate. The Agency will provide an updated REMS document to the ARC, and is attached to this review.

As the Medication Guide has been removed as an element of the REMS program, information for women who cannot get pregnant would no longer be available in the REMS materials. Therefore, the *Guide for Females who Can Get Pregnant* should be retitled to the *Guide for Female Patients*, to inform stakeholders that information for all female patients is now included in this material. Consequently, the Agency has added content for females who cannot get pregnant into the *Guide for Females who Can Get Pregnant* as this information was previously only reflected in the MG. The Agency will provide an updated redlined *Guide for Female Patients* to the ARC, and is attached to this review.

The *Prescriber Guide for the Ambrisentan REMS Program* should be retitled to the *Ambrisentan REMS Prescriber and Pharmacy Guide*. The guide should be revised to include information about the role of inpatient and outpatient pharmacies in the Ambrisentan REMS Program as this information is not currently included in other REMS materials. The pharmacy information should be added as a separate section to the existing Prescriber Guide. The *Prescriber and Pharmacy Guide* may be modeled after the

publicly available *Adempas REMS Program Prescriber and Pharmacy Guide*; this advice will be communicated to the Sponsor group.

The ARC proposed to add a Pharmacy Enrollment Form to document certification of all pharmacies (inpatient and outpatient) in the REMS Program. While the Agency found the addition of a Pharmacy Enrollment Form acceptable, we requested the development of two separate forms for inpatient pharmacy enrollment and outpatient pharmacy enrollment². The ARC responded appropriately to this request. However, further revisions are required to these forms to include stakeholder attestations and align the forms with current agency thinking on naming of REMS. The Agency will provide updated redlined *Inpatient and Outpatient Pharmacy Enrollment Forms* to the ARC, and they are attached to this review.

Additionally, the Agency's current thinking has changed regarding both the naming of the REMS program and referencing the titles of REMS materials within the content of the REMS materials themselves. Using the term "Program" as part of the name of the REMS program or materials is no longer necessary. For example, the "Ambrisentan REMS Program" should be revised to read the "Ambrisentan REMS". In addition, repeating the prefix "Ambrisentan REMS Program" or "Ambrisentan REMS" when referencing REMS materials within the body of REMS materials is redundant making the information longer and more difficult to read through. The notation of "Ambrisentan REMS" should be removed from the name of individual materials when they are referenced within the body of another REMS material, however, the materials should retain "Ambrisentan REMS" in their name when the title is serving as a heading (e.g., at the top of the material, the title page, or listed on the REMS website) so the material is identifiable. For example, the actual *Prescriber Enrollment Form* should be titled *Ambrisentan REMS Prescriber Enrollment Form* for ease of identification. If the *Prescriber Enrollment Form* is referenced to in the *Pharmacy Guide*, it should be referenced as the *Prescriber Enrollment form*. The Agency has made most of these revisions in the redlined materials which are attached to this review.

Furthermore, the ARC has not provided a proposed website that shows the full functionality of the program. Working screenshots showing both format and content must be provided to the Agency for review.

Finally, DRISK agrees with all other previously mentioned changes, additions, and deletions made to the REMS Document, appended materials, and supporting document unless otherwise noted.

5 Conclusion and Recommendations

The proposed REMS requires further changes to be acceptable.

Comments for the ARC are provided in Section 6.

6 Comments to the ARC

The following comments and attached red-lined documents are based on the Agency's review of the proposed Ambrisentan shared system REMS submitted under NDA 022081 and ANDAs 208354, 208252, and 209509. In order to facilitate further review, we ask that you respond to these comments within 14 business days.

A. General Comments

1. We have provided a revised REMS document for the Ambrisentan shared system REMS. The REMS document continues to undergo final clearance and therefore is subject to further revision by the Agency.
2. The Agency's current thinking has changed regarding both the naming of the REMS program and referencing the titles of REMS materials within the content of the REMS materials themselves.
 - a. Revise "Ambrisentan REMS Program" to read "Ambrisentan REMS" as using the term "Program" as part of the name of the *Ambrisentan* REMS is no longer necessary.
 - b. Remove the notation of "Ambrisentan REMS" from the name of individual materials when they are referenced within the body of another REMS material. These materials, however, should retain "Ambrisentan REMS" in their name when the title is serving as a heading (e.g., at the top of the material, the title page, or listed on the REMS website) so the material is identifiable. For example, the actual *Prescriber Enrollment Form* should be titled *Ambrisentan REMS Prescriber Enrollment Form* for ease of identification. If the *Prescriber Enrollment Form* is referenced to in the *Pharmacy Guide*, it should be referenced as the *Prescriber Enrollment form*. The repetition of the prefix "Ambrisentan REMS Program" or "Ambrisentan REMS" when referencing REMS materials within the body of REMS materials is redundant makes the information longer and more difficult to read through. Please see attached redlined materials.

B. Appended Materials

1. Guide for Females Who Can Get Pregnant

The *Guide for Females who Can Get Pregnant* should be retitled to the *Guide for Female Patients*. As the Medication Guide has been removed as an element of the REMS program, information for women who cannot get pregnant is no longer available in the REMS materials. Therefore, the *Guide for Females who Can Get Pregnant* should be retitled to the *Guide for Female Patients*, to inform stakeholders that information for all female patients is now included in this material. Consequently, the Agency has added content for females who cannot get pregnant into the *Guide for Females who Can Get Pregnant* as this information was previously only reflected in the Medication Guide. Please see attached redlined materials.

2. Prescriber Guide

The *Prescriber Guide for the Ambrisentan REMS Program* should be retitled to the *Ambrisentan REMS Prescriber and Pharmacy Guide*. Revise this guide to include information about the role

of inpatient and outpatient pharmacies in the Ambrisentan shared system REMS as this information is not currently included in other REMS materials. The pharmacy information should be added as a separate section to the existing Prescriber Guide. The *Prescriber and Pharmacy Guide* may be modeled after the publicly available *Adempas REMS program Prescriber and Pharmacy Guide* available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Adempas_2017-01-17_Prescriber_and_Pharmacy_Guide.pdf

3. Website

Provide screenshots showing both format, content, and functionality of the website to the Agency for review as the provided screenshots do not show functionality.

7 Appendices

7.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

1. Gilead Pharmaceuticals. Proposed REMS for ambrisentan. NDA 022081 S-039, dated 4/24/18
2. SigmaPharm. Proposed REMS for ambrisentan. ANDA 208354 , dated 4/24/18
3. Watson. Proposed REMS for ambrisentan. ANDA 208252 , dated 4/24/18
4. Par. Proposed REMS for ambrisentan. ANDA 209509, dated 4/24/18
5. Gilead. Letairis REMS. NDA 022082 approved on 10/29/09 and last modified on 09/27/17.
6. Sheppard J, Blair J. DRISK. REMS Review for Ambrisentan SS REMS, dated April 3, 2018.

7.2 APPENDED MATERIALS

Ambrisentan REMS Document

Prescriber Enrollment and Agreement Form

Outpatient Pharmacy Enrollment Form

Inpatient Pharmacy Enrollment Form

Prescriber Guide

Guide for Females Who Can Get Pregnant

Patient Enrollment and Consent Form

Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form

REMS Website

¹ Sheppard J, Blair J. DRISK. REMS Review for Ambrisentan SS REMS, dated April 4, 2018.

² Sheppard J, Blair J. DRISK. REMS Review for Ambrisentan SS REMS, dated April 4, 2018.

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/s/

JACQUELINE E SHEPPARD
08/10/2018

LAURA A ZENDEL
08/10/2018

JAMIE C WILKINS PARKER
08/10/2018

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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|--------------------------------------|--|-------------|
| Applicant/Application Numbers | Gilead Pharmaceuticals | NDA 022081 |
| | SigmaPharm Laboratories | ANDA 208354 |
| | Watson Laboratories | ANDA 208252 |
| | Par Pharmaceutical | ANDA 209509 |
| OSE RCM # | 2015-1623 | |
| Reviewer Name | Jacqueline Sheppard, PharmD | |
| Health Communications Analyst | Joan Blair, RN, MPH | |
| Team Leader | Leah Hart, PharmD | |
| Deputy Division Director | Jamie Wilkins Parker, PharmD | |
| Review Completion Date | April 3, 2018 | |
| Subject | Evaluation of proposed shared REMS for ambrisentan | |
| Established Name | Ambrisentan | |
| OND Review Division | Division of Cardiovascular and Renal Products | |
| Therapeutic Class | Endothelin Receptor Antagonist | |
| Dosage Form | 5 mg and 10 mg tablets for oral administration | |

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates the proposed shared system (SS) risk evaluation and mitigation strategy (REMS) for ambrisentan initially submitted by the Ambrisentan REMS Consortium (ARC) comprised of Gilead Pharmaceuticals^a, Watson Laboratories^b, SigmaPharm Laboratories^c, and Par Pharmaceuticals^d on December 1, 2017 and December 5, 2017. The Sponsors' proposed SS REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU) and a timetable for submission of assessments. The elements of the proposed SS are the same as the currently approved Letairis REMS. The submission also constitutes a REMS modification for Letairis, the reference listed drug (RLD), for which a RiskMAP was approved under NDA 022081 on June 15, 2007. The Letairis REMS was subsequently approved on October 29, 2009 and last modified on September 27, 2017.

The ARC proposed to update the existing Letairis REMS to create a shared system by removing the information specific to Gilead and the branded product and by creating a new shared REMS website and Ambrisentan REMS Coordinating Center. Additionally, the ARC has proposed to add a Pharmacy Enrollment Form to document certification of all pharmacies (inpatient and outpatient) in the REMS Program. As inpatient and outpatient pharmacies will serve patients with different clinical needs and have different monitoring capabilities, the Agency has separated inpatient and outpatient requirements in the shared system REMS document which will require the development of two separate forms for pharmacy enrollment. The REMS and appended materials however require revisions.

Additionally, the MG should be removed as an element of the REMS; but will continue to be included as part of product labeling and distributed as required under 21 CFR 208. This program has a patient directed material that is focused on the REMS associated risks, as compared with the MG, which is a patient-directed educational tool that communicates additional risks associated with ambrisentan.

As such, additional revisions are required to the proposed SS REMS document, Appended Materials, and Supporting Document to be acceptable.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed shared risk evaluation and mitigation strategy (REMS) for ambrisentan received on December 1, 2017 and December 5, 2017 submitted by Gilead Pharmaceuticals, Letairis, new drug application (NDA) 022081 and the following abbreviated new drug applications (ANDAs): Watson (ANDA 208252), SigmaPharm (ANDA 208354), and Par (ANDA 209509) herein referred to in this review as the Ambrisentan REMS Consortium (ARC). The Sponsors' proposed SS REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU)

^a Submitted December 5, 2017 (RLD)

^b Submitted December 1, 2017

^c Submitted December 5, 2017

^d Submitted December 5, 2017

and a timetable for submission of assessments. The elements of the proposed SS are the same as the currently approved Letairis REMS.

2 Background

2.1 PRODUCT INFORMATION

Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. It is currently available in 5 mg and 10 mg tablets for oral administration and is dosed at 5 mg once daily, with or without tadalafil 20 mg once daily. At four week intervals, either the dose of Letairis or tadalafil can be increased to Letairis 10 mg or tadalafil 40 mg.

The RLD, Letairis was originally approved on June 15, 2007 under 21 CFR 314.520 Subpart H approval with a Risk Minimization Action Plan (RiskMAP) due to teratogenicity and hepatotoxicity. Letairis was deemed to have a REMS in effect^e because the product had a RiskMAP with restrictive elements. The REMS for Letairis was subsequently approved on October 29, 2009 and was last modified on September 27, 2017. The most recently approved REMS for Letairis consists of a MG, ETASU, an implementation plan, and a timetable for submission of assessments. The goals of the currently approved REMS are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Letairis.
2. To minimize the risk of fetal exposures and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Letairis
 - a. Females who are pregnant must not be prescribed Letairis
 - b. Females taking Letairis must not become pregnant

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for the proposed SS REMS relevant to this review:

- 10/29/2009: The REMS for Letairis was approved for PAH. The REMS consisted of a MG, ETASU, an implementation plan, and a timetable for submission of assessments.
- 03/23/2015: The Agency sent a Pre- Approval REMS Notification letter to Watson Pharmaceuticals.
- 06/15/2015: The Agency sent a Pre- Approval REMS Notification letter to Sigma Pharmaceuticals.

^e Section 909 of FDAAA provides that drugs approved with restrictive elements before FDAAA was enacted were deemed to have REMS. Sponsors of these products were required to submit proposed REMS by September 21, 2008.

- 02/06/2017: The Agency sent a Pre- Approval REMS Notification letter to Par Pharmaceuticals
- 06/15/2015: The Agency sent a Pre- Approval REMS Notification letter to Watson Pharmaceuticals
- 12/01/2017: A shared system REMS was submitted by Watson Pharmaceuticals including proposed changes to the REMS Document, Supporting Document, and Appended Materials
- 12/05/2017: A shared system REMS was submitted by Gilead Pharmaceuticals (as Prior Approval Supplement 39), SigmaPharm Laboratories, and Par Pharmaceuticals which included proposed changes to the REMS Document, Supporting Document, and Appended Materials

3 Results of the Review of the ARC's Proposed REMS

The ARC's proposed shared system REMS includes the same elements to assure safe use (ETASU) as those in the currently approved Letairis REMS. The Sponsors' have revised the Letairis REMS document and appended materials to reflect the shared system Ambrisentan REMS Program. DRISK finds these changes acceptable except where noted below.

Further, the Agency has made changes to the REMS document. These changes are provided in the attached redlined document. In addition to changes in the presentation of goals, DRISK has determined that a change in certain aspects of the proposed operational design are necessary to ensure that the minimal requirements are met to ensure the safe use of the ambrisentan in an inpatient setting.

As such, the proposed SSS REMS document, Appended Materials, and Supporting Document require additional revisions to be acceptable.

3.1 REMS GOAL

The ARC's proposed goal are the same as those in the currently approved Letairis REMS and are stated below:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for ambrisentan
2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed ambrisentan
 - a. Females who are pregnant must not be prescribed ambrisentan
 - b. Females taking ambrisentan must not become pregnant

Reviewer Comments: *The proposed ARC goals are the same as in the currently approved Letairis REMS. However, the Agency is revising the presentation of the REMS goals to align with Agency current thinking*

as presented in the October 2017 FDA Draft Guidance ([Format and Content of a REMS Document^f](#)). Please see comments in Section 4.

3.2 REMS DOCUMENT

- The ARC proposes to update the existing Letairis REMS document to create a shared system REMS by removing the information specific to Gilead and the branded product Letairis, and creating a new shared REMS website and Ambrisentan REMS Coordinating Center.

Reviewer Comments: DRISK finds this approach to create a SS REMS document acceptable. However, there are still outstanding items in the REMS document that need to be addressed. Please see comments in Section 4.

3.3 REMS MATERIALS

The proposed Ambrisentan SS REMS includes the same appended materials as the Letairis REMS with the addition of a Pharmacy Enrollment Form. The appended materials have all been revised to reflect the shared Ambrisentan REMS Program. However, all materials will need to be revised to align with the comments on the REMS Document that is provided with this review. Additional comments are provided below.

3.3.1 Pharmacy Enrollment Form

- The ARC has included a Pharmacy Enrollment Form to certify pharmacies into the Ambrisentan REMS Program.

Reviewer Comments: We agree with the addition of a Pharmacy Enrollment Form. However due to differences in the requirements to ensure safe use in the inpatient and outpatient pharmacy settings, this will require the development of separate forms for inpatient pharmacy enrollment and outpatient pharmacy enrollment. Please see comments in Section 4.

3.3.2 Website

- The ARC has provided a proposed website in Microsoft Word format. The provided website shows the creation of a shared system with the removal of references to the branded Letairis..

Reviewer Comments: The the provided website does not provide enough working screenshots. Please see comments in Section 4.

3.4 REMS SUPPORTING DOCUMENT

The ARC updated the Supporting Document per changes to the program, however additional changes are required to align with the comments on the REMS Document that are provided with this review.

^f <https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf>

Furthermore, the language below should be added to the Supporting Document in order to add provisions for the ANDA applicant holders to participate in the assessments:

“As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of the REMS and whether the goals or elements should be modified. The REMS assessment plan proposed by the Ambrisentan Sponsors is a shared assessment that addresses the elements that the FDA requested along with the methodology for each element”.

4 Discussion

This review by the Division of Risk Management (DRISK) evaluates the proposed shared system (SS) risk evaluation and mitigation strategy (REMS) for ambrisentan proposed by the members of the Ambrisentan REMS Consortium (ARC) on December 1 and December 5, 2017. This submission also constitutes a REMS modification for Letairis, the RLD. The goals of the shared system have not changed from the currently approved RLD Letairis REMS. The goal of the Ambrisentan REMS will continue to be to inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Letairis and to minimize the risk of fetal exposures and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Letairis; however, it was determined the goals should be revised to more accurately reflect current Agency thinking on formatting of REMS goals and better align the REMS goals and objectives. As such, the Agency is revising the presentation of the REMS goals in the REMS document as presented in the October 2017 FDA Draft Guidance (*Format and Content of a REMS Document*⁸).

The ARC proposes to update the existing Letairis REMS document to create a shared system REMS by removing the information specific to Gilead and the branded product product, Letairis, and creating a new shared REMS website and Ambrisentan REMS Coordinating Center. DRISK finds this approach acceptable. However, DRISK has determined that a change in certain aspects of the proposed operational design are necessary to ensure that the minimal requirements are met to ensure the safe use of the ambrisentan in an inpatient setting, as there is currently no inpatient provision in the approved program for inpatient enrollment.

In the currently approved Letairis REMS Program, there is no Pharmacy Enrollment Form as the programmatic structure (the RLD had implemented the program with exclusive use of specialty pharmacies) did not necessitate them. The ARC has proposed to add a Pharmacy Enrollment Form to document certification of all pharmacies (inpatient and outpatient) in the REMS Program. DRISK finds the addition of a Pharmacy Enrollment Form acceptable, as Agency current thinking is that all pharmacies certifying in a program should enroll via an enrollment form to ensure that the authorized representative is attesting to all requirements in the program. However, inpatient and outpatient pharmacies will serve patients with different clinical needs and have different monitoring capabilities,

⁸ <https://www.fda.gov/downloads/Drugs/.../Guidances/UCM184128.pdf>

therefore the necessary requirements for patients in an inpatient setting to receive ambrisentan are: 1)the patient is enrolled or will be enrolled prior to discharge and, 2) is under the care of a certified prescriber. As such, the Agency has separated inpatient and outpatient requirements in the shared system REMS document. This will require the development of two separate forms for inpatient pharmacy enrollment and outpatient pharmacy enrollment, as their attestations will differ. The Inpatient Pharmacy Enrollment form may be modeled after the publicly available Tracleer REMS program Inpatient Pharmacy Enrollment form; this advice will be communicated to the Sponsor group.

The Agency will provide a revised REMS document with this review that includes the Inpatient Pharmacy Requirements that are not in the currently approved Letairis REMS, but are proposed by the Agency. All appended materials should be revised to align with the comments on the provided REMS document. Additionally, the revised REMS document has been converted into the new REMS format.

Additionally, the ARC has provided a proposed website in Microsoft Word format. While the website shows the creation of a shared system with the removal of references to the branded Letairis, the provided website does not provide enough working screenshots to show the functionality of the program. Working screenshots showing both format and content must be provided to the Agency for review.

The ARC updated the Supporting Document per changes to the program, however additional changes are required to align with the comments on the REMS Document that are provided with this review. The language below should be added to the Supporting Document in order to add provisions for the ANDA applicant holders to participate in the assessments:

The statement “As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of the REMS and whether the goals or elements should be modified. The REMS assessment plan proposed by the Ambrisentan Sponsors is a shared assessment that addresses the elements that the FDA requested along with the methodology for each element”.

Furthermore, the MG should be removed as an element of the REMS; but will continue to be included as part of product labeling and distributed as required under 21 CFR 208. This program has a patient directed material that is focused on the REMS associated risks, as compared with the MG, which is a patient-directed educational tool that communicates additional risks associated with ambrisentan.

DRISK agrees with all other previously mentioned changes, additions, and deletions made to the REMS Document, appended materials, and supporting document unless otherwise noted.

5 Conclusion and Recommendations

DRISK does not agree with all of the ARC’S proposals for an Ambrisentan SS REMS.

Comments for the RLD and ANDA Sponsors are provided in Sections 6 and 7.

6 Comments to Gilead

The comments in the attached red-lined documents are based on the Agency's review of the proposed SS REMS for ambrisentan submitted under NDA 022081. In order to facilitate further review, we ask that you respond to these comments within 14 business days.

A. General Comments

1. We have provided a revised REMS document for the Ambrisentan REMS shared system. The document has not undergone final clearance and is subject to further revision by the Agency.
2. Revise all materials to align with the comments on the provided REMS Document.

B. REMS Document

1. Submit a bifurcated REMS with your submission. The REMS document should be presented with the Letairis REMS following immediately by the Shared System REMS in one continuous document. The presence of bifurcated REMS will imply that the shared system document will be the effective governing document when the first ANDA referencing ambrisentan receives full approval. To further clarify the implementation date of the shared system, a textbox is added to the SS documents to provide additional clarity. See the attached red-lined REMS document.

C. Appended Materials

1. Pharmacy Enrollment Form

The Pharmacy Enrollment Form should be separated into an Inpatient Pharmacy Enrollment Form and an Outpatient Pharmacy Enrollment Form. As inpatient and outpatient pharmacies will serve patients different with different clinical needs and have different monitoring capabilities, the minimally necessary requirements for patients in an inpatient setting to receive ambrisentan safely are that the patient is enrolled or will be enrolled prior to discharge and is under the care of a certified prescriber. As such, the Agency has separated inpatient and outpatient requirements in the shared system REMS document. This will require the development of two separate forms for inpatient pharmacy enrollment and outpatient pharmacy enrollment as their attestations will differ. The Inpatient Pharmacy Enrollment form should be modeled after the publically available Tracleer REMS program Inpatient Pharmacy Enrollment Form.

2. Website

Provide working screenshots showing both format and content to the Agency for review as the provided screenshots do not show the functionality of the Shared Ambrisentan program.

3. Supporting Document

Add the following language to the Supporting Document in order to add provisions for the ANDA applicant holders to participate in the assessments:

“As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of the REMS and whether the goals or elements should be modified. The REMS assessment plan proposed by the Ambrisentan Sponsors is a shared assessment that addresses the elements that the FDA requested along with the methodology for each element”.

D. Medication Guide

The MG should be removed as an element of the REMS; but will continue to be included as part of product labeling and distributed as required under 21 CFR 208. This program has a patient directed material that is focused on the REMS associated risks, as compared with the MG, which is a patient-directed educational tool that communicates additional risks associated with ambrisentan.

7 Comments to the ANDA Holders

The comments in the attached red-lined documents are based on the Agency’s review of the proposed SS REMS for ambrisentan submitted under ANDAs 208354, 208252, and 209509. In order to facilitate further review, we ask that you respond to these comments within 14 business days.

A. General Comments

1. We have provided a revised REMS document for the Ambrisentan REMS shared system. The document is still undergoing internal clearance and is subject to further revision by the Agency.
2. Revise all materials to align with the comments on the provided REMS Document.

B. Appended Materials

1. Pharmacy Enrollment Form

The Pharmacy Enrollment Form should be separated into an Inpatient Pharmacy Enrollment Form and an Outpatient Pharmacy Enrollment Form in order to align with the REMS document. As inpatient and outpatient pharmacies will serve patient with different clinical needs and have different monitoring capabilities, the necessary requirements for patients in an inpatient setting to receive ambrisentan safely are that the patient is enrolled or will be enrolled prior to discharge and is under the care of a certified prescriber. As such, the Agency has separated inpatient and outpatient requirements in the shared system REMS document. This will require the development of two separate forms for inpatient pharmacy enrollment and outpatient pharmacy enrollment as their attestations will differ. The Inpatient Pharmacy Enrollment form should be modeled after the publically available Tracleer REMS program Inpatient Pharmacy Enrollment Form.

2. Website

Provide working screenshots showing both format and content to the Agency for review as the provided screenshots do not show the functionality of the Shared Ambrisentan program.

3. Supporting Document

Add the following language to the Supporting Document in order to add provisions for the ANDA applicant holders to participate in the assessments:

“As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of the REMS and whether the goals or elements should be modified. The REMS assessment plan proposed by the Ambrisentan Sponsors is a shared assessment that addresses the elements that the FDA requested along with the methodology for each element”.

C. Medication Guide

The MG should be removed as an element of the REMS; but will continue to be included as part of product labeling and distributed as required under 21 CFR 208. This program has a patient directed material that is focused on the REMS associated risks, as compared with the MG, which is a patient-directed educational tool that communicates additional risks associated with ambrisentan.

8 Appendices

8.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

1. Gilead Pharmaceuticals. Proposed REMS for ambrisentan. NDA 022081 S-039, dated 12/5/2017
2. SigmaPharm. Proposed REMS for ambrisentan. ANDA 208354 , dated 12/5/2017
3. Watson. Proposed REMS for ambrisentan. ANDA 208252 , dated 12/1/2017
4. Par. Proposed REMS for ambrisentan. ANDA 209509, dated 12/5/2017
5. Gilead. Letairis REMS. NDA 022082 approved on 10/29/09 and last modified on 09/27/17.

8.2 APPENDED MATERIALS

REMS Document

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

/s/

JACQUELINE E SHEPPARD
04/03/2018

CYNTHIA L LACIVITA on behalf of JAMIE C WILKINS PARKER
04/04/2018

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022081Orig1s039

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Anderson, Alycia

From: Killen, Monique
Sent: Friday, August 10, 2018 4:42 PM
To: April.Given@gilead.com
Cc: Kang, Sue; Lyons, Darrell; Anderson, Alycia; Amchin, Wayne
Subject: FW: Ambrisentan ARC Interim Comments
Attachments: guide-for-female.patients-FDA.docx; prescriber-pharm-guide-FDA.docx; prescriber-enrollment-FDA.docx; pharmacy-outpatient-enroll.FDA.docx; pharmacy-inpatient-enroll.FDA.docx; rems-website-FDA.docx; reproductive-annual-verification-FDA.docx; patient-enroll.FDA.docx; ARC SS REMS Document 8.7.18.docx

Follow Up Flag: Follow up
Flag Status: Flagged

Hi April Given,

Please refer to your April 24, 2018, amendment to your proposed Single Shared System REMS submission for Ambrisentan.

We reviewed the Ambrisentan Shared System REMS document, REMS supporting document, and REMS materials. The following interim comments and attached red-lined documents are based on the Agency's review of the proposed Ambrisentan shared system REMS submitted under NDA 022081 and ANDAs 208354, 208252, and 209509. In order to facilitate further review, we ask that you respond to these comments within 14 business days.

A. General Comments

1. We have provided a revised REMS document for the Ambrisentan shared system REMS. The REMS document continues to undergo final clearance and therefore is subject to further revision by the Agency.
2. The Agency's current thinking has changed regarding both the naming of the REMS program and referencing the titles of REMS materials within the content of the REMS materials themselves.
 - a. Revise "Ambrisentan REMS Program" to read "Ambrisentan REMS" as using the term "Program" as part of the name of the *Ambrisentan* REMS is no longer necessary.
 - b. Remove the notation of "Ambrisentan REMS" from the name of individual materials when they are referenced within the body of another REMS material. These materials, however, should retain "Ambrisentan REMS" in their name when the title is serving as a heading (e.g., at the top of the material, the title page, or listed on the REMS website) so the material is identifiable. For example, the actual *Prescriber Enrollment Form* should be titled *Ambrisentan REMS Prescriber Enrollment Form* for ease of identification. If the *Prescriber Enrollment Form* is referenced to in the *Pharmacy Guide*, it should be referenced as the *Prescriber Enrollment form*. The repetition of the prefix "Ambrisentan REMS Program" or "Ambrisentan REMS" when referencing REMS materials within the body of REMS materials is redundant makes the information longer and more difficult to read through. Please see attached redlined materials.

B. Appended Materials

1. Guide for Females Who Can Get Pregnant

The *Guide for Females who Can Get Pregnant* should be retitled to the *Guide for Female Patients*. As the Medication Guide has been removed as an element of the REMS program, information for women who cannot

get pregnant is no longer available in the REMS materials. Therefore, the *Guide for Females who Can Get Pregnant* should be retitled to the *Guide for Female Patients*, to inform stakeholders that information for all female patients is now included in this material. Consequently, the Agency has added content for females who cannot get pregnant into the *Guide for Females who Can Get Pregnant* as this information was previously only reflected in the Medication Guide. Please see attached redlined materials.

2. Prescriber Guide

The *Prescriber Guide for the Ambrisentan REMS Program* should be retitled to the *Ambrisentan REMS Prescriber and Pharmacy Guide*. Revise this guide to include information about the role of inpatient and outpatient pharmacies in the Ambrisentan shared system REMS as this information is not currently included in other REMS materials. The pharmacy information should be added as a separate section to the existing Prescriber Guide. The *Prescriber and Pharmacy Guide* may be modeled after the publicly available *Adempas REMS program Prescriber and Pharmacy Guide* available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Adempas_2017-01-17_Prescriber_and_Pharmacy_Guide.pdf

3. Website

Provide screenshots showing both format, content, and functionality of the website to the Agency for review as the provided screenshots do not show functionality.

Attachments

Ambrisentan REMS Document
Prescriber Enrollment and Agreement Form
Outpatient Pharmacy Enrollment Form
Inpatient Pharmacy Enrollment Form
Prescriber Guide
Guide for Females Who Can Get Pregnant
Patient Enrollment and Consent Form
Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form
REMS Website

Please respond to Alycia Anderson via e-mail no later than **August 30, 2018**, and remember to submit your formal response to the application.

Please confirm receipt of this email.

Kind regards,
Monique (on behalf of Alycia Anderson)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALYCIA C ANDERSON
08/15/2018

Anderson, Alycia

From: Anderson, Alycia
Sent: Wednesday, April 04, 2018 11:30 AM
To: 'April Given'
Cc: Ayalasomayajula, Vasantha; Jenkins, Darrell
Subject: Ambrisentan SSS - NDA - Information Request
Attachments: ARC Bifurcated REMS Document (RLD).docx

Good morning, April.

The comments in the attached red-lined documents are based on the Agency's review of the proposed SS REMS for ambrisentan submitted under NDA 022081.

A. General Comments

1. We have provided a revised REMS document for the Ambrisentan REMS shared system. The document is still undergoing internal clearance and is subject to further revision by the Agency.
2. Revise all materials to align with the comments on the provided REMS Document.

B. REMS Document

1. Submit a bifurcated REMS with your submission. The REMS document should be presented with the Letairis REMS following immediately by the Shared System REMS in one continuous document. The presence of bifurcated REMS will imply that the shared system document will be the effective governing document when the first ANDA referencing Letairis receives full approval. To further clarify the implementation date of the shared system, a textbox is added to the SS documents to provide additional clarity. See the attached red-lined REMS document.

C. Appended Materials

1. Pharmacy Enrollment Form

The Pharmacy Enrollment Form should be separated into an Inpatient Pharmacy Enrollment Form and an Outpatient Pharmacy Enrollment Form. As inpatient and outpatient pharmacies serve different patient acuities and have different monitoring capabilities, the minimally necessary requirements for patients in an inpatient setting to receive ambrisentan safely are that the patient is enrolled or will be enrolled prior to discharge and is under the care of a certified prescriber. As such, the Agency has separated inpatient and outpatient requirements in the shared system REMS document. This will require the development of two separate forms for inpatient pharmacy enrollment and outpatient pharmacy enrollment as their attestations will differ. The Inpatient Pharmacy Enrollment form should be modeled after the publically available Tracleer REMS program Inpatient Pharmacy Enrollment Form.

2. Website

Provide working screenshots showing both format and content to the Agency for review as the provided screenshots do not show the functionality of the Shared Ambrisentan program.

3. Supporting Document

Add the following language to the Supporting Document in order to add provisions for the ANDA applicant holders to participate in the assessments:

"As required under section 505-1(g)(3)(A) of the FDCA, assessments of an approved REMS must assess the extent to which the elements to assure safe use are meeting the goals of the REMS and whether the goals or elements should be modified. The REMS assessment plan proposed by the Ambrisentan Sponsors is a shared

assessment that addresses the elements that the FDA requested along with the methodology for each element”.

D. Medication Guide

The MG should be removed as an element of the REMS; but will continue to be included as part of product labeling and distributed as required under 21 CFR 208. This program has a patient directed material that is focused on the REMS associated risks, as compared with the MG, which is a patient-directed educational tool that communicates additional risks associated with ambrisentan.

Please provide a written response by **COB (ET), Tuesday, April 24, 2018**. Please submit the responses formally to the individual NDA application.

Please confirm receipt of this e-mail.

Best Regards,

Alycia Anderson

~~~~~

Alycia Anderson, CCRP

Regulatory Health Project Manager

OMPT/CDER/OSE/PMS

10903 New Hampshire Avenue

WO #22, Room 4435

Silver Spring, MD 20903

(240) 402-4270 (Desk)

(240) 678-7111 (Cell)

[alycia.anderson@fda.hhs.gov](mailto:alycia.anderson@fda.hhs.gov)

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**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/  
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ALYCIA C ANDERSON  
04/04/2018

## Lyons, Darrell

---

**From:** Lyons, Darrell  
**Sent:** Tuesday, January 02, 2018 10:23 AM  
**To:** Alison Blaus (Alison.Blaus@gilead.com)  
**Cc:** Jenkins, Darrell; Ayalasomayajula, Vasantha; Wachter, Lori; Phillips, Chantal  
**Subject:** Information Request (IR) for the Ambrisentan REMS Consortium (ARC)

Dear Ms. Blaus,

In the proposed REMS Supporting Document submitted December 5, 2017, certified pharmacies are to provide daily product dispensing data for FRP to the Ambrisentan REMS Coordinating Center. Provide the rationale for the collection of this data including the purpose for the data collection and how the data will be used by the Ambrisentan REMS Consortium. Your response should outline the rationale for the inpatient and outpatient pharmacy settings.

Please submit a response to the respective applications by **January 10, 2018**.

Best regards,

Darrell Lyons, BSN, RN  
Commander, USPHS  
Safety Regulatory Project Manager  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
U.S. Food and Drug Administration  
Tel: (301) 796-4092  
[darrell.lyons@fda.hhs.gov](mailto:darrell.lyons@fda.hhs.gov)



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**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/  
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DARRELL LYONS  
01/02/2018