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, 8.6).**
- **For all female patients, Letairis is available only through a restricted program called the Letairis Risk Evaluation and Mitigation Strategy (REMS) (5.2).**

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

• Indications and Usage (1)	10/2015
• Dosage and Administration (2.1)	10/2015
• Warnings and Precautions (5.3)	10/2015

----------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 (8.3).
- Not recommended in patients with moderate or severe hepatic impairment (8.8).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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 (8.6)]*.

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 (8.6)].*

3 DOSAGE FORMS AND STRENGTHS

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

- 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, 8.6)]*.

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, 8.6)].*

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 (8.6)].*
- 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

	Placebo (N=132)	**Letairis (N=261)**	
Adverse Reaction	**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

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