

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: POTENTIAL LIVER INJURY AND CONTRAINDICATION IN PREGNANCY

See full prescribing information for complete boxed warning.

- Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS and serious liver injury has been reported with related drugs.
- Monitor liver aminotransferases monthly and discontinue LETAIRIS if >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN or by signs or symptoms of liver dysfunction.
- May cause fetal harm if taken during pregnancy (4.1).
- Must exclude pregnancy before the start of treatment (2.2).
- Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed (2.2, 5.5).

RECENT MAJOR CHANGES

- Boxed Warning, 05/2009
- Dosage and Administration, Women of Childbearing Potential (2.2), 05/2009
- Contraindications, Pregnancy Category X (4.1), 05/2009
- Warnings and Precautions, Hematological Changes (5.2) 07/2009
- Warnings and Precautions, Decreased Sperm Counts (5.4) 07/2009
- Warnings and Precautions, Prescribing and Distribution Program for LETAIRIS (5.5) 05/2009
- Deleted: Warnings and Precautions, Co-administration of LETAIRIS and Cyclosporine A (5.4) 07/2009
- Deleted: Warnings and Precautions, Co-administration of LETAIRIS with Strong CYP3A and 2C19 Inhibitors (5.5) 07/2009

INDICATIONS AND USAGE

LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening (1).

DOSAGE AND ADMINISTRATION

- Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated (2.1).

- Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests (2.2, 5.5).
- Not recommended in patients with moderate or severe hepatic impairment (2.3).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.2).
- Fluid retention may require intervention (5.3).
- Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (5.4).

ADVERSE REACTIONS

- Most common placebo-adjusted adverse reactions are peripheral edema, nasal congestion, sinusitis, flushing, palpitations, nasopharyngitis, abdominal pain, and constipation (6.1).
- Fluid retention was identified as an adverse reaction during postapproval use of LETAIRIS (6.2).

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

DRUG INTERACTIONS

- No clinically significant interactions of LETAIRIS with warfarin, sildenafil, tadalafil, omeprazole (CYP2C19 inhibitor), ketoconazole (strong CYP3A inhibitor), digoxin, ethinylestradiol, or norethisterone have been observed (7.2).
- Other potential interactions are not well characterized, but, based on *in vitro* data, interactions with P-glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), and uridine 5'-diphosphate glucuronosyltransferases (UGTs) would be expected (7.3).

USE IN SPECIFIC POPULATIONS

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

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

Revised: 07/2009

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FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations >3 x ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3 x ULN has been accompanied by bilirubin elevations >2 x ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin >2 x ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

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

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP [see *Warnings and Precautions (5.5)*].

1 INDICATIONS AND USAGE

LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

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

Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH). Liver function tests should be measured prior to initiation and during treatment with LETAIRIS [see *Warnings and Precautions* (5.1)].

2.2 Women of Childbearing Potential

Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS [see *Contraindications* (4.1) and *Warnings and Precautions* (5.5)].

2.3 Pre-existing Hepatic Impairment

LETAIRIS is not recommended in patients with moderate or severe hepatic impairment [see *Use in Specific Populations* (8.7)]. There is no information on the use of LETAIRIS in patients with mild hepatic impairment; however, exposure to ambrisentan may be increased in these patients.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Pregnancy Category X

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

LETAIRIS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be

excluded before the initiation of treatment with LETAIRIS and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed [see *Dosage and Administration (2.2)*, and *Warnings and Precautions (5.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potential Liver Injury (see BOXED WARNING)

Treatment with endothelin receptor antagonists has been associated with dose-dependent liver injury manifested primarily by elevation of serum aminotransferases (ALT or AST), but sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferases greater than 3-times the upper limit of normal ($>3 \times \text{ULN}$) and total bilirubin $>2 \times \text{ULN}$ is a marker for potentially serious hepatic injury.

Liver function tests were closely monitored in all clinical studies with LETAIRIS. For all LETAIRIS-treated patients (N=483), the 12-week incidence of aminotransferases $>3 \times \text{ULN}$ was 0.8% and $>8 \times \text{ULN}$ was 0.2%. For placebo-treated patients, the 12-week incidence of aminotransferases $>3 \times \text{ULN}$ was 2.3% and $>8 \times \text{ULN}$ was 0.0%. The 1-year rate of aminotransferase elevations $>3 \times \text{ULN}$ with LETAIRIS was 2.8% and $>8 \times \text{ULN}$ was 0.5%. One case of aminotransferase elevations $>3 \times \text{ULN}$ has been accompanied by bilirubin elevations $>2 \times \text{ULN}$.

Liver chemistries must be measured prior to initiation of LETAIRIS and at least every month thereafter. If there are aminotransferase elevations $>3 \times \text{ULN}$ and $\leq 5 \times \text{ULN}$, they should be re-measured. If the confirmed level is $>3 \times \text{ULN}$ and $\leq 5 \times \text{ULN}$, reduce the daily dose or interrupt treatment and continue to monitor every two weeks until the levels are $<3 \times \text{ULN}$. If there are aminotransferase elevations $>5 \times \text{ULN}$ and $\leq 8 \times \text{ULN}$, LETAIRIS should be discontinued and monitoring should continue until the levels are $<3 \times \text{ULN}$. LETAIRIS can then be re-initiated with more frequent measurement of aminotransferase levels. If there are aminotransferase elevations $>8 \times \text{ULN}$, treatment should be stopped and re-initiation should not be considered.

LETAIRIS is not recommended in patients with elevated aminotransferases ($>3 \times \text{ULN}$) at baseline because monitoring liver injury may be more difficult. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or increases in bilirubin $>2 \times \text{ULN}$, LETAIRIS treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

5.2 Hematological Changes

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with LETAIRIS. These decreases were observed within the first few weeks of treatment with

LETAIRIS, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving LETAIRIS in the 12-week placebo-controlled studies was 0.8 g/dL.

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

Measure hemoglobin prior to initiation of LETAIRIS, at one month, and periodically thereafter. Initiation of LETAIRIS therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing LETAIRIS.

5.3 Fluid Retention

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

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

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

5.4 Decreased Sperm Counts

In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data [see *Nonclinical Toxicology (13.1)*] from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as LETAIRIS have an adverse effect on spermatogenesis.

5.5 Prescribing and Distribution Program for LETAIRIS

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

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

- Read the Prescribing Information (PI) and Medication Guide for LETAIRIS.
- Enroll all patients in LEAP and re-enroll patients after the first 12 months of treatment and annually thereafter.
- Review the LETAIRIS Medication Guide and patient education brochure(s) with every patient.
- Educate patients on the risks of LETAIRIS, including the risks of hepatotoxicity and teratogenicity [see *Boxed Warning*].
- Educate and counsel women of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom.

Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring.

Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom.

Partner's vasectomy must be used along with a hormone method or a barrier method [see *Boxed Warning, Contraindications (4.1)*].

- Order and review liver function tests (including aminotransferases and bilirubin) prior to initiation of LETAIRIS treatment and monthly during treatment.
- For women of childbearing potential, order and review a pregnancy test prior to initiation of LETAIRIS treatment and monthly during treatment.
- Counsel patients who fail to comply with the program requirements.
- Notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

See *Boxed Warning* for discussion of potential liver injury and *Warnings and Precautions (5.2)* for discussion of hematological changes.

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

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

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

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

Adverse event	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
Palpitations	3 (2)	12 (5)	3
Nasopharyngitis	1 (1)	9 (3)	2
Abdominal pain	1 (1)	8 (3)	2
Constipation	2 (2)	10 (4)	2
Dyspnea	4 (3)	11 (4)	1
Headache	18 (14)	38 (15)	1

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

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent. Fewer patients receiving LETAIRIS had adverse events related to liver function tests compared to placebo.

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

The incidence of treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for LETAIRIS (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension was similar for placebo (7%; 9/132 patients) and for LETAIRIS (5%; 13/261 patients).

6.2 Postmarketing Experience

The following adverse reactions were identified during postapproval use of LETAIRIS: Fluid retention [see *Warnings and Precautions (5.3)*], heart failure (associated with fluid retention), hypersensitivity (e.g., angioedema, rash), and anemia.

Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 *In vitro* studies

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, uridine 5'-diphosphate glucuronosyltransferases (UGTs), 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of the Organic Anion Transport Protein (OATP), and a substrate but not an inhibitor of P-gp.

7.2 *In vivo* studies

Co-administration of ambrisentan with the following drugs does not result in clinically relevant changes in ambrisentan exposure:

- Ketoconazole
- Omeprazole
- Sildenafil
- Tadalafil

Co-administration of ambrisentan does not change the exposure to the following drugs:

- Warfarin
- Digoxin
- Sildenafil

- Tadalafil
- Ethinylestradiol/Norethisterone

In a clinical study in healthy subjects, steady state dosing with ambrisentan 10 mg did not significantly affect the single-dose pharmacokinetics of the ethinylestradiol or norethisterone components of a combined oral contraceptive (Ortho-Novum 1/35). Based on this pharmacokinetic study, ambrisentan would not be expected to affect significantly the exposure to other estrogen- or progestin-based contraceptives.

7.3 Unknown

The drug interaction potential of ambrisentan is not fully characterized because *in vivo* drug interaction studies have not been conducted with the following types of drugs: strong inducers of CYP3A and 2C19 (rifampin), inducers of UGTs and P-gp (rifampin), strong inhibitors of the transporters P-gp (cyclosporine A) and OATP (cyclosporine A, rifampin, ritonavir). Because ritonavir, cyclosporine A and rifampin can impact the above enzymes and transporters involved in the disposition of ambrisentan, clinically significant changes in the exposure to ambrisentan cannot be excluded.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications (4.1)*].

8.3 Nursing Mothers

It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving LETAIRIS is not recommended. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testicle size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17x, 51x, and 170x (low, mid, high dose, respectively) the maximum oral human dose of 10 mg on a mg/mm² basis.

8.4 Pediatric Use

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

8.5 Geriatric Use

In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were ≥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

The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is *in vitro* and *in vivo* evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan [see *Clinical Pharmacology* (12.3)]. LETAIRIS is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of LETAIRIS in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients [see *Dosage and Administration* (2.3)].

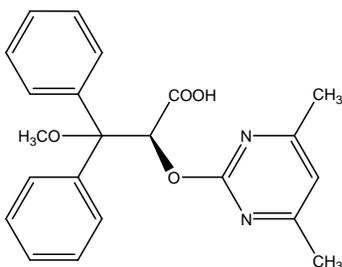
10 OVERDOSAGE

There is no experience with overdosage of LETAIRIS. The highest single dose of LETAIRIS administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention.

11 DESCRIPTION

LETAIRIS is the brand name for ambrisentan, an endothelin receptor antagonist that is selective for the endothelin type-A (ET_A) receptor. The chemical name of ambrisentan is (+)-(2S)-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 pKa of 4.0. Ambrisentan is practically insoluble in water and in aqueous solutions at low pH. Solubility increases in aqueous solutions at higher pH. In the solid state ambrisentan is very stable, is not hygroscopic, and is not light sensitive.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

Ambrisentan is a high affinity ($K_i=0.011$ 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.

12.3 Pharmacokinetics

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

Ambrisentan is metabolized by CYP3A, CYP2C19 and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of the Organic Anion Transport Protein (OATP), and a substrate but not an inhibitor of P-gp. Drug interactions might be expected because of these factors; however, clinically relevant interactions with drugs utilizing these metabolic pathways have not been demonstrated [see *Drug Interactions (7)*].

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 PAH (64%) or PAH associated with connective tissue disease (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 Capacity

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

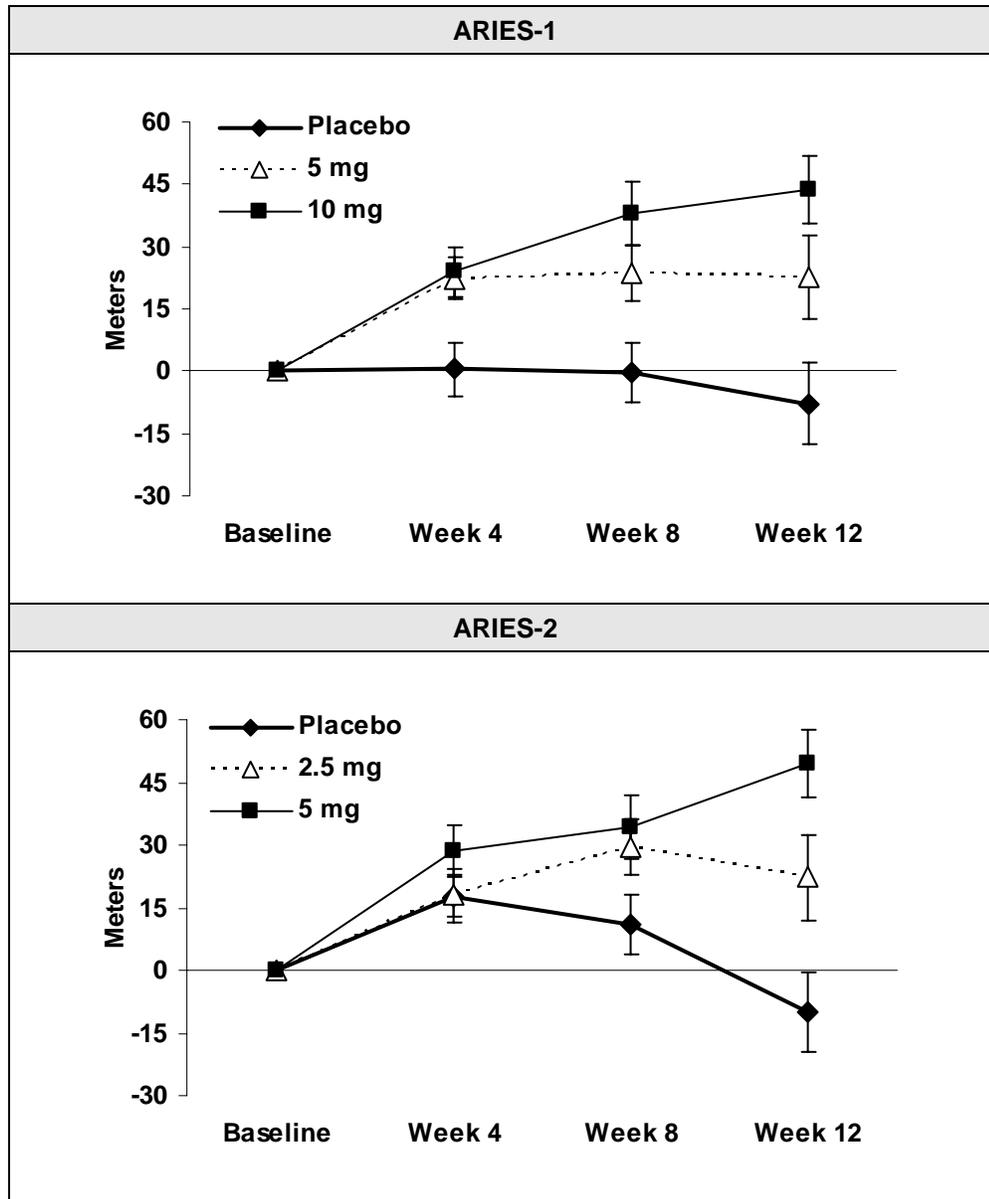
Table 2 Changes from Baseline in 6-Minute Walk Distance (meters)

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

Mean ± standard deviation

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

Figure 2 Mean Change in 6-minute Walk Distance



Mean change from baseline in 6-minute walk distance in the placebo and LETAIRIS groups. Values are expressed as mean \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 PAH. The results of such subgroup analyses must be interpreted cautiously.

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

Clinical Worsening

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

Table 3 Time to Clinical Worsening

	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, Fisher exact test	–	0.044	–	0.006
p-value, Log-rank test	–	0.030	–	0.005

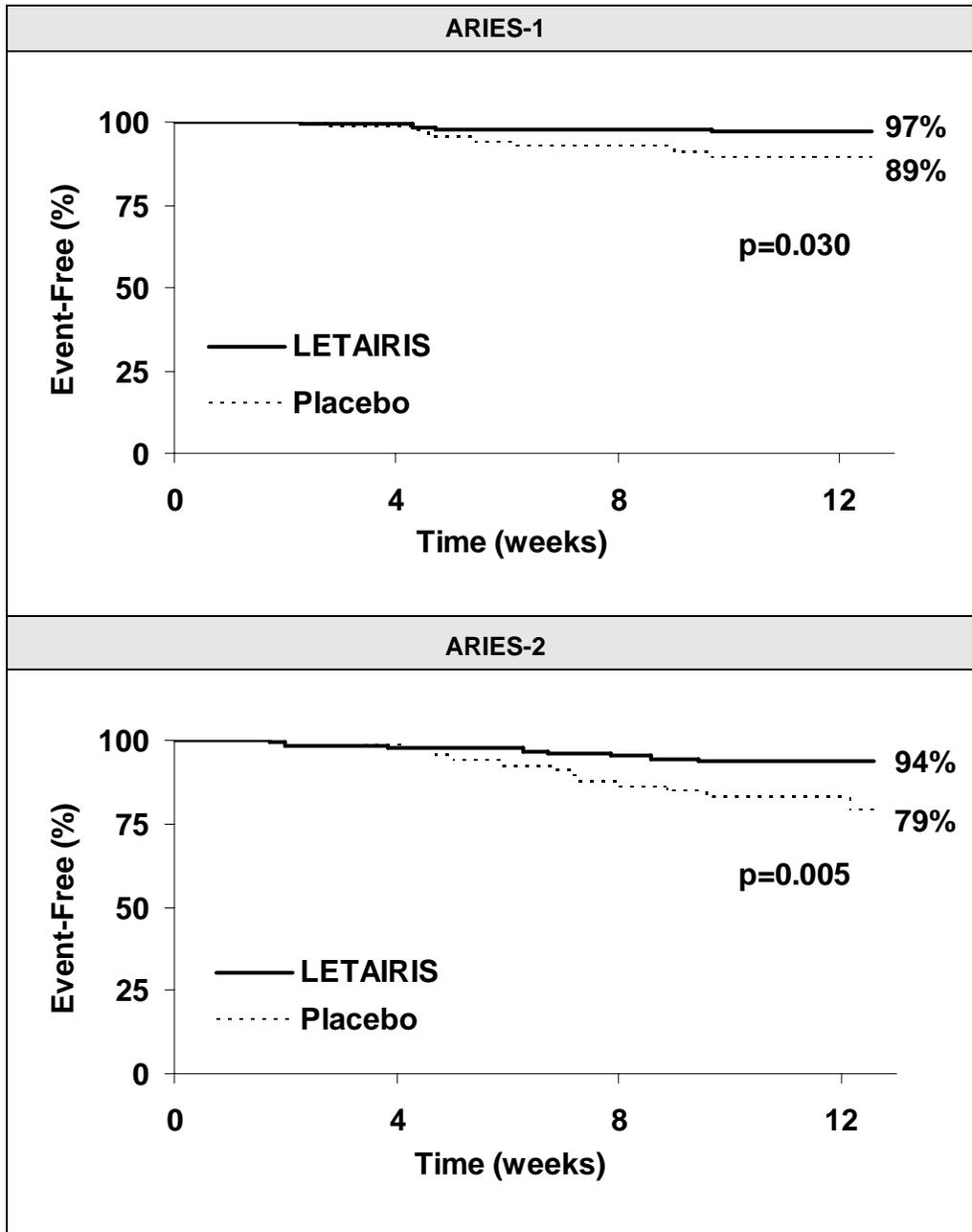
Intention-to-treat population

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 3 Time to Clinical Worsening



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

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

14.2 Long-term Treatment of PAH

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

14.3 Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Liver Function Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x upper limit of normal (ULN) were treated with LETAIRIS. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on LETAIRIS 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow-up of 13 months and with 50% of patients increasing the dose of LETAIRIS to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that LETAIRIS led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that LETAIRIS may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

Rx only

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

17 PATIENT COUNSELING INFORMATION

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

17.1 Importance of Preventing Pregnancy

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

Women of childbearing potential should be informed of the importance of monthly pregnancy tests and the need to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom. Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring. Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom. Partner's vasectomy must be used along with a hormone method or a barrier method.

Patients should be instructed to immediately contact their physician if they suspect they may be pregnant [see Warnings and Precautions (5.5)].

17.2 Adverse Liver Effects

Patients should be advised of the importance of monthly liver function testing and instructed to immediately report any symptoms of potential liver injury (such as

anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) to their physician.

17.3 Hematological Change

Patients should be advised of the importance of hemoglobin testing.

17.4 Administration

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

17.5 FDA-Approved Medication Guide

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

Gilead Sciences, Inc., Foster City, CA 94404

Revised July 2009

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GS22-081-005

Medication Guide
LETAIRIS® (le-TAIR-is)
Tablets
(ambrisentan)

Read this Medication Guide before you start taking LETAIRIS and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about LETAIRIS?

- **Possible liver injury.**

LETAIRIS can cause liver injury. You must have a blood test to check your liver function before you start LETAIRIS and each month after that. Your doctor will order these blood tests. (See “What are the possible side effects of LETAIRIS?” for information about the signs of liver problems.) **Tell your doctor if you have had moderate or severe liver problems, including liver problems while taking other medicines.**

- **Serious birth defects.**

LETAIRIS can cause serious birth defects if taken during pregnancy. Women must not be pregnant when they start taking LETAIRIS or become pregnant during treatment. Women who are able to get pregnant must have a negative pregnancy test before beginning treatment with LETAIRIS and each month during treatment. Your doctor will decide when to do the test, depending on your menstrual cycle.

Women who are able to get pregnant must use two acceptable forms of birth control at the same time, during LETAIRIS treatment and for one month after stopping LETAIRIS. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. **Do not have unprotected sex. Tell your doctor right away if you miss a menstrual period or think you may be pregnant.**

LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). To receive LETAIRIS, you must talk to your doctor, understand the benefits and risks of LETAIRIS, and agree to all of the instructions in the LEAP program.

What is LETAIRIS?

LETAIRIS is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.

LETAIRIS can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

Who should not take LETAIRIS?

Do not take LETAIRIS if:

- **you are pregnant, plan to become pregnant, or become pregnant during treatment with LETAIRIS. LETAIRIS can cause serious birth defects.** (See “What is the most important information I should know about LETAIRIS?”) Serious birth defects from LETAIRIS happen early in pregnancy.
- **your blood tests show possible liver injury.**

Tell your doctor about all your medical conditions and all the medicines you take including prescription and nonprescription medicines. LETAIRIS and other medicines may affect each other causing side effects. Do not start any new medicines until you check with your doctor.

LETAIRIS has not been studied in children.

How should I take LETAIRIS?

LETAIRIS will be mailed to you by a specialty pharmacy. Your doctor will give you complete details.

- Take LETAIRIS exactly as your doctor tells you. Do not stop taking LETAIRIS unless your doctor tells you.
- You can take LETAIRIS with or without food.
- Do not split, crush or chew LETAIRIS tablets.
- It will be easier to remember to take LETAIRIS if you take it at the same time each day.
- If you take more than your regular dose of LETAIRIS, call your doctor right away.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take two doses at the same time to make up for a missed dose.
- During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

What should I avoid while taking LETAIRIS?

- **Do not get pregnant** while taking LETAIRIS. (See the serious birth defects section of "What is the most important information I should know about LETAIRIS?") If you miss a menstrual period, or think you might be pregnant, call your doctor right away.
- **Breastfeeding is not recommended** while taking LETAIRIS. It is not known if LETAIRIS can pass through your milk and harm your baby.

What are the possible side effects of LETAIRIS?

Serious side effects of LETAIRIS include:

- **Possible liver injury.** (See "What is the most important information I should know about LETAIRIS?") Call your doctor right away if you have any of these symptoms of liver problems: loss of appetite, nausea, vomiting, fever, unusual tiredness, abdominal (stomach area) pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.
- **Serious birth defects.** (See "What is the most important information I should know about LETAIRIS?")
- **Swelling all over the body** (fluid retention) can happen within weeks after starting LETAIRIS. Tell your doctor right away if you have any unusual weight gain, tiredness, or trouble breathing while taking LETAIRIS. These may be symptoms of a serious health problem. You may need to be treated with medicine or need to go to the hospital.
- **Sperm count reduction.** Reduced sperm counts have been observed in some men taking a drug similar to LETAIRIS, an effect which might impair their ability to father a child. Tell your doctor if remaining fertile is important to you.

The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of hands, legs, ankles and feet (peripheral edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)
- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache

Allergic reactions (rash, swelling of the face, lips, mouth, tongue, or throat which may cause difficulty in swallowing or breathing) have been reported infrequently.

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of LETAIRIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LETAIRIS?

Store LETAIRIS at 59 °F to 86 °F (15 °C to 30 °C), in the package it comes in.

Keep LETAIRIS and all medicines out of the reach of children.

General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LETAIRIS for a condition for which it was not prescribed. Do not give LETAIRIS to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LETAIRIS. If you would like more information, ask your doctor. You can ask your doctor or pharmacist for information about LETAIRIS that is written for healthcare professionals.

For more information, call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com.

What are the ingredients in LETAIRIS?

Active ingredient: ambrisentan

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.

Revised July 2009

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

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GS22-081-005

LEAP Prescriber Enrollment and Agreement Form

To be enrolled into LEAP, complete and fax the front of this form. **FAX:** 1-888-882-4035

Prescriber Information

First Name _____ Middle Initial _____ Last Name _____ Suffix _____

Specialty _____ Name of Facility _____ Office Contact _____

Address _____ City _____ State _____ ZIP _____

E-mail _____ Phone (____) _____ Fax (____) _____

State License # _____ NPI # _____ DEA # _____

Prescriber Agreement

By signing below, you signify your understanding of the risks of Letairis[®] (ambrisentan) treatment and your obligation as a LETAIRIS prescriber to educate your patients about these risks, counsel them on risk reduction, monitor them appropriately, and report adverse events to LEAP. Specifically, you attest to the following:

- I have read the full prescribing information for LETAIRIS.
- I agree to enroll all patients in LEAP and re-enroll patients after the first 12 months of treatment and annually thereafter by completing and submitting a new patient enrollment form.
- I will discuss the risks of LETAIRIS with each patient prior to prescribing LETAIRIS, including the risks of hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility.
- I will review the patient Medication Guide and patient education brochure with each patient prior to prescribing LETAIRIS.
- I will order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests (for female patients of childbearing potential*) prior to initiating treatment with LETAIRIS and monthly during treatment.
- I will educate and counsel female patients of childbearing potential to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom.
 - Acceptable hormone methods include: progesterone injectables, progesterone implants, combination oral contraceptives, transdermal patch, and vaginal ring.
 - Acceptable barrier methods include: diaphragm (with spermicide), cervical cap (with spermicide), and the male condom.
 - Partner's vasectomy must be used along with a hormone method or a barrier method.
 - All women of childbearing potential should undergo contraceptive counseling, with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.
- I will measure hemoglobin and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter.
- I will counsel patients who fail to comply with the program requirements.
- I will notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment.

Prescriber Signature _____ **Date** _____

If you have any questions, please call 1-866-664-LEAP (5327).

Please visit www.letairis.com or www.gilead.com for more information.

*See reverse side for definition of a female patient of childbearing potential.



*The prescriber must determine if a female patient is of childbearing potential before enrolling her in LEAP.

- Women of childbearing potential must use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment.
 - If the patient has a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed.
 - Women who do not choose one of these methods should always use two acceptable forms of contraception— one hormone method and one barrier method, or two barrier methods where one method is the male condom.
 - All women of childbearing potential should undergo contraceptive counseling, with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.

Acceptable Contraception Methods		
Methods to Use by Themselves	Combination Methods	
	Hormone Methods Choose one and use with a barrier method	Barrier Methods Use both OR choose one and use with a hormone method
Intrauterine devices (IUDs) <ul style="list-style-type: none"> • Copper T 380A IUD • LNg 20 IUS (progesterone IUD) Tubal sterilization	Estrogen and progesterone <ul style="list-style-type: none"> • Oral contraceptives • Transdermal patch • Vaginal ring Progesterone only <ul style="list-style-type: none"> • Injection • Implant 	<ul style="list-style-type: none"> • Diaphragm with spermicide OR <ul style="list-style-type: none"> • Cervical cap with spermicide • Male condom (with or without spermicide)
	Partner's vasectomy must be used along with a hormone method or a barrier method.	

Definition of a Female Patient of Childbearing Potential

A female patient of childbearing potential is a non-menopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This includes pubertal females who have not yet had a menses (premenarchal, Tanner Stage 3), peri-menopausal women who have had a spontaneous menses in the last 12 months and women who have had a tubal sterilization.

Pre-pubertal females (Tanner Stages 1 and 2) are not considered to be of childbearing potential. These patients should be carefully monitored for changes in childbearing potential status during LETAIRIS treatment. Notify LEAP if the patient's childbearing potential status changes.

Definition of Menopause

Menopause can be assumed to have occurred in a woman when there is either:

- Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed), OR
- Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified healthcare provider (i.e., "spontaneous menopause," which occurs in the United States at a mean age of 51.5 years).
 - Hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:
 - If age ≥ 54 years and with the absence of normal menses: Serum Follicle Stimulating Hormone (FSH) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;
 - If age < 54 years and with the absence of normal menses: Negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the post-menopausal range, depressed estradiol (E2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

There is no need to fax this side of the form.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.



Prescriber Information

INDICATION: LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.



Letairis[®]
ambrisentan

5 mg and 10 mg Tablets

About LEAP

LEAP is a program to help you and your patients learn about the risks of Letairis® (ambrisentan), including the serious risks of liver injury and birth defects.

Because of the risk of liver injury, and in an effort to make the chance of fetal exposure to LETAIRIS as small as possible, LETAIRIS may be prescribed only through LEAP by calling 1-866-664-LEAP (5327).

LEAP works by:

- Providing information to prescribers on the risks of LETAIRIS
- Providing comprehensive education to patients and assistance with obtaining LETAIRIS
- Requiring enrollment of both prescriber and patient in LEAP
- Controlling dispensing through a specialized distribution network (specialty pharmacies)

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.

LEAP Overview

The Prescriber:

- Completes a Prescriber Enrollment and Agreement Form and faxes it to LEAP
- Counsels each patient on the risks of LETAIRIS treatment
- Reviews the patient Medication Guide and patient education brochure with the patient
- Orders and reviews liver function tests (including aminotransferases and bilirubin) and pregnancy tests prior to initiating treatment with LETAIRIS and monthly during treatment
- Orders and reviews hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter
- Assists patient with choosing a specialty pharmacy
- Completes a Patient Enrollment and Consent Form for each patient and faxes it to LEAP
- Re-enrolls patients after the first 12 months of treatment and annually thereafter

LEAP:

- Enters every LETAIRIS prescriber and patient in the LEAP database
- Along with the specialty pharmacy, LEAP confirms insurance coverage or investigates alternative sources of reimbursement or assistance
- Sends patient information to the chosen specialty pharmacy

The Specialty Pharmacy:

- Files the insurance claim
- Contacts patients each month to obtain confirmation that they completed the required testing
- Answers questions and provides information about LETAIRIS
- Ships LETAIRIS to the patient

Prescriber Enrollment

Healthcare professionals who wish to prescribe LETAIRIS must enroll in LEAP by completing a Prescriber Enrollment and Agreement Form that states they will comply with the program requirements.

The prescriber agrees to:

- Read the LETAIRIS full prescribing information and understand the risks of LETAIRIS.
- Use the patient Medication Guide and patient education brochure to educate the patient and discuss the risks of LETAIRIS.
- Enroll all patients in LEAP and re-enroll patients after the first 12 months of treatment and annually thereafter.
- Discuss with female patients of childbearing potential the need to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment.
 - If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed.
 - Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom. Please refer to page 5 for a complete list of acceptable contraception methods.
 - All women of childbearing potential should undergo contraceptive counseling, with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.

Acceptable Contraception Methods		
Methods to Use by Themselves	Combination Methods	
	Hormone Methods Choose one and use with a barrier method	Barrier Methods Use both OR choose one and use with a hormone method
Intrauterine devices (IUDs) • Copper T 380A IUD • LNG 20 IUS (progesterone IUD) Tubal sterilization	Estrogen and progesterone • Oral contraceptives • Transdermal patch • Vaginal ring Progesterone only • Injection • Implant	• Diaphragm with spermicide OR Cervical cap with spermicide • Male condom (with or without spermicide)
Partner's vasectomy must be used along with a hormone method or a barrier method.		

- Order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests prior to initiating treatment with LETAIRIS and monthly during treatment.
- Order and review hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter.
- Counsel patients who fail to comply with the program requirements and notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment.

Prescribers must complete, sign, and fax the Prescriber Enrollment and Agreement Form. **FAX:** 1-888-882-4035.

Patient Enrollment

LETAIRIS is available only to patients enrolled in LEAP. To enroll a patient in LEAP, complete the following steps:

1. Fill out the Patient Enrollment and Consent Form completely and legibly.
2. Use the patient Medication Guide and patient education brochure to educate the patient about the risks of LETAIRIS.
3. Discuss with female patients of childbearing potential* the need to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. If the patient has a tubal sterilization or chooses to use a Copper T380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed. Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom. Refer to page 5 for a complete list of acceptable contraception methods.
4. Schedule monthly liver function tests (including aminotransferases and bilirubin) and pregnancy tests.
5. Help the patient choose a specialty pharmacy.
6. Confirm that the patient has agreed to comply with program requirements and has signed the form where indicated.
7. Provide the LEAP Patient Enrollment Guide to the patient.
8. Sign and fax the completed Patient Enrollment and Consent Form. **FAX:** 1-888-882-4035.
9. Keep the original form with the patient's records.
10. Re-enroll patients after the first 12 months of treatment and annually thereafter. You will be reminded when re-enrollment is required.

Please see the following pages for risks of hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and fluid retention; potential risk of reduced male fertility; coadministration with cyclosporine A; and adverse reactions.

*The prescriber must determine if a female patient is of childbearing potential before enrolling her in LEAP.

Definition of a Female Patient of Childbearing Potential

A female patient of childbearing potential is a non-menopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This includes pubertal females who have not yet had a menses (premenarchal, Tanner Stage 3), peri-menopausal women who have had a spontaneous menses in the last 12 months and women who have had a tubal sterilization.

Pre-pubertal females (Tanner Stages 1 and 2) are not considered to be of childbearing potential. These patients should be carefully monitored for changes in childbearing potential status during LETAIRIS treatment. Notify LEAP if the patient's childbearing potential status changes.

Definition of Menopause

Menopause can be assumed to have occurred in a woman when there is either:

- Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in “surgical menopause” and occurring at the age at which the procedure was performed), OR
- Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified healthcare provider (i.e., “spontaneous menopause,” which occurs in the United States at a mean age of 51.5 years).
 - Hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:
 - If age ≥ 54 years and with the absence of normal menses: Serum Follicle Stimulating Hormone (FSH) level elevated to within the post-menopausal range based on the laboratory reference range where the hormonal assay is performed;
 - If age < 54 years and with the absence of normal menses: Negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the post-menopausal range, depressed estradiol (E2) level in the post-menopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.

LETAIRIS Risk Information

Education is a key component of risk management. Prescribers must review the LETAIRIS full prescribing information to prepare for patient counseling. This brochure is only a summary of some of the important information about LETAIRIS.

Indication

LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Risk of Hepatotoxicity

Treatment with ERAs has been associated with dose-dependent liver injury manifested primarily by elevation of serum aminotransferases (ALT or AST), but sometimes accompanied by abnormal liver function (elevated bilirubin). The combination of aminotransferases greater than 3 times the upper limit of normal ($>3 \times \text{ULN}$) and total bilirubin $>2 \times \text{ULN}$ is a marker for potentially serious hepatic injury. Liver function tests (including aminotransferases and bilirubin) must be measured prior to initiating treatment with LETAIRIS and monthly during treatment.

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

Risk of Teratogenicity

LETAIRIS may cause fetal harm when administered to a pregnant woman. Pregnancy must be excluded prior to the initiation of LETAIRIS treatment and prevented thereafter.

Female patients of childbearing potential must agree to the following:

- A negative pregnancy test prior to treatment initiation is required.
- Monthly pregnancy testing during LETAIRIS treatment.
- Use of highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment.

–If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS for pregnancy prevention, no additional contraception is needed.

–Women who do not choose one of these methods should always use two acceptable forms of contraception—one hormone method and one barrier method, or two barrier methods where one method is the male condom. Refer to page 5 for a complete list of acceptable contraception methods.

- Undergo contraceptive counseling, with either the prescriber or another designated healthcare practitioner trained in contraceptive counseling.
- Report any delay in onset of menses or any other reason to suspect pregnancy during treatment to the prescriber immediately.

If pregnancy is suspected for any reason, a pregnancy test must be performed. If the pregnancy test is positive, the prescriber and patient should discuss the risk of pregnancy, the potential risk to the fetus, and the patient's options. The prescriber must notify LEAP of any pregnancies that occur during treatment or within 30 days of discontinuation.

There are no data regarding the use of LETAIRIS in pregnant women.

LETAIRIS Risk Information

Risk of Decreases in Hemoglobin Concentration and Hematocrit

Decreases in hemoglobin concentration and hematocrit have followed administration of other ERAs and were observed in clinical studies with LETAIRIS. These decreases were observed within the first few weeks of treatment with LETAIRIS, and stabilized thereafter.

Measure hemoglobin prior to initiation of LETAIRIS, at 1 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.

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 with placebo (see Adverse Reactions on next page). Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients.

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.

Potential Risk of Reduced Male Fertility

In a 6-month study of another ERA, 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 from ERAs, it cannot be excluded that ERAs such as LETAIRIS have an adverse effect on spermatogenesis.

Adverse Reactions

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

Prescriber Responsibilities

- Read the LETAIRIS full prescribing information and understand the risks of LETAIRIS
- Complete the LEAP Prescriber Enrollment and Agreement Form
- Enroll all patients in LEAP and re-enroll patients after the first 12 months of treatment and annually thereafter
- Use the patient Medication Guide and patient brochure to educate patients about the risks of LETAIRIS treatment
- Discuss with female patients of childbearing potential the need to use highly reliable contraception during LETAIRIS treatment and for one month after stopping treatment. Refer to page 5 for a complete list of acceptable contraception methods.
- Order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests prior to initiating treatment with LETAIRIS and monthly during treatment
- Order and review hemoglobin concentrations and hematocrit prior to initiating treatment with LETAIRIS, at 1 month, and periodically thereafter
- Counsel patients who fail to comply with the program requirements and notify LEAP of any adverse events, including liver injury, or if any patient becomes pregnant during LETAIRIS treatment

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.

LETAIRIS can only be supplied through specialty pharmacies.

Participating specialty pharmacies include:

- Accredo
- Aetna Specialty Pharmacy
- CVS Caremark
- CIGNA Tel-Drug
- CuraScript
- Fairview Specialty Pharmacy
- Kaiser Specialty Pharmacy (CA residents only)
- PrecisionRx Specialty Solutions
- Walgreens Specialty Pharmacy
- WellCare Specialty Pharmacy

Important Safety Information

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations $>3x$ ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations $>3x$ ULN has been accompanied by bilirubin elevations $>2x$ ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the postmarketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases ($>3x$ ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $>2x$ ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

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

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

If you have questions or would like additional information, please call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.



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The Letairis logo features a stylized orange and yellow wave above the word "Letairis" in a large, bold, purple font, with "ambrisentan" in a smaller, purple font below it. At the bottom, it says "5 mg and 10 mg Tablets" in a smaller, purple font.

Patient Enrollment Guide

For starting therapy with LETAIRIS

INDICATION: LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.



Letairis[®]
ambrisentan

5 mg and 10 mg Tablets

What is the LETAIRIS Education and Access Program (LEAP)?

LEAP is a program to help you learn about the risks of Letairis® (ambrisentan), including the serious risks of liver injury and birth defects.

Your doctor enrolls you in LEAP. Once you are enrolled, you will get your LETAIRIS prescription through a specialty pharmacy that you and your doctor choose.

Why use a specialty pharmacy?

Specialty pharmacies provide products and services for patients with certain diseases. Only specialty pharmacies carry LETAIRIS. You and your doctor will choose the specialty pharmacy. LEAP makes sure the specialty pharmacy you choose is covered by your insurance. Your insurance company may require you to use a particular specialty pharmacy.

Your specialty pharmacy can help:

- File your insurance claims
- Resolve insurance problems
- Refill your prescription
- Answer questions and provide information about LETAIRIS
- Ship your medicine

Participating specialty pharmacies:

- Accredo
- Aetna Specialty Pharmacy
- CVS Caremark
- CIGNA Tel-Drug
- CuraScript
- Fairview Specialty Pharmacy
- Kaiser Specialty Pharmacy (CA residents only)
- PrecisionRx Specialty Solutions
- Walgreens Specialty Pharmacy
- WellCare Specialty Pharmacy

How do I enroll in LEAP?

Enrolling in LEAP is easy. Follow these steps with your doctor.

Read all the patient information about LETAIRIS and LEAP.

Talk with your doctor about the risks of LETAIRIS.
Ask questions. Make sure you understand what you need to do.

You and your doctor choose a specialty pharmacy to supply LETAIRIS.

Your doctor fills out the enrollment form.
After you read and sign it, your doctor sends it to LEAP.

LEAP helps ensure the specialty pharmacy you choose is the
best option for you and then sends them your information.

Your specialty pharmacy ships LETAIRIS to you each month.
Before each shipment, you will be called to make sure
that you have completed the tests you need and to review
important information about LETAIRIS and LEAP.

What do I need to do for LEAP?

LETAIRIS can cause liver injury and serious birth defects if taken during pregnancy. Therefore, women must not be pregnant when they start LETAIRIS or become pregnant during treatment.

Before you start LETAIRIS you must:

- Have a blood test to check your liver and red blood cells.
- Have a negative pregnancy test (for women who are able to get pregnant).
Your doctor will decide when to do the test, depending on your menstrual cycle.

You must complete all of the tests your doctor orders.

While taking LETAIRIS:

- You must have monthly blood tests to check your liver.
- For women who are able to get pregnant, you must also:
 - Have monthly pregnancy tests. Your doctor orders the tests.
 - Use contraception during LETAIRIS treatment and for one month after stopping LETAIRIS treatment if you had a period in the past year or have not gone through menopause.
 - Read the LETAIRIS information about preventing pregnancy and choosing contraception.
 - Use the table below. You may choose one method from the first column to use by itself. Or you may choose two other contraception methods to use in combination each time you have intercourse.

Acceptable Contraception Methods		
Methods to Use by Themselves	Combination Methods	
	Hormone Methods Choose one and use with a barrier method	Barrier Methods Use both OR choose one and use with a hormone method
Intrauterine devices (IUDs) <ul style="list-style-type: none"> • Copper T 380A IUD • LNg 20 IUS (progesterone IUD) Tubal sterilization	Estrogen and progesterone <ul style="list-style-type: none"> • Oral contraceptives • Transdermal patch • Vaginal ring Progesterone only <ul style="list-style-type: none"> • Injection • Implant 	<ul style="list-style-type: none"> • Diaphragm with spermicide OR <ul style="list-style-type: none"> • Cervical cap with spermicide • Male condom (with or without spermicide)
Partner's vasectomy must be used along with a hormone method or a barrier method.		

Work with your healthcare practitioner to choose the contraception methods that are best for you.

Important Safety Information

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations $>3x$ ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations $>3x$ ULN has been accompanied by bilirubin elevations $>2x$ ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the postmarketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases ($>3x$ ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $>2x$ ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

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

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

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.

Please visit www.letairis.com or www.gilead.com for more information.

If you have questions or concerns, talk to your doctor.



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Letairis[®]
ambrisentan

5 mg and 10 mg Tablets


Letairis[®]
ambrisentan

5 mg and 10 mg Tablets

LETAIRIS Therapy

What you need to know

INDICATION: LETAIRIS is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.





Letairis[®]
ambrisentan

5 mg and 10 mg Tablets

What do I need to do to get started?

- 1. You and your doctor will review the patient Medication Guide and patient education brochure to help you learn about the risks of Letairis[®] (ambrisentan), including the serious risks of liver injury and birth defects.**
- 2. To start treatment with LETAIRIS, your doctor must enroll you in the LETAIRIS Education and Access Program (LEAP). If you are not already enrolled in LEAP, ask your doctor for more information.**

LEAP is a program to help you learn about the risks of LETAIRIS, including the serious risks of liver injury and birth defects.
- 3. Once you are enrolled in LEAP, you will get your LETAIRIS prescription through a specialty pharmacy. Only specialty pharmacies carry LETAIRIS.**
- 4. The specialty pharmacy ships LETAIRIS to you each month. Before each shipment, you will be called to make sure you have completed the tests you need and to review important information about LETAIRIS and LEAP.**

LETAIRIS® (le-TAIR-is) Tablets (ambrisentan)

Read this Medication Guide before you start taking LETAIRIS and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about LETAIRIS?

- **Possible liver injury.**

LETAIRIS can cause liver injury. You must have a blood test to check your liver function before you start LETAIRIS and each month after that. Your doctor will order these blood tests. (See “What are the possible side effects of LETAIRIS?” for information about the signs of liver problems.) **Tell your doctor if you have had moderate or severe liver problems, including liver problems while taking other medicines.**

- **Serious birth defects.**

LETAIRIS can cause serious birth defects if taken during pregnancy. Women must not be pregnant when they start taking LETAIRIS or become pregnant during treatment. Women who are able to get pregnant must have a negative pregnancy test before beginning treatment with LETAIRIS and each month during treatment. Your doctor will decide when to do the test, depending on your menstrual cycle.

Women who are able to get pregnant must use two acceptable forms of birth control at the same time, during LETAIRIS treatment and for one month after stopping LETAIRIS. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. **Do not have unprotected sex. Tell your doctor right away if you miss a menstrual period or think you may be pregnant.**

LETAIRIS is available only through a restricted program called the LETAIRIS Education and Access Program (LEAP). To receive LETAIRIS, you must talk to your doctor, understand the benefits and risks of LETAIRIS, and agree to all of the instructions in the LEAP program.

What is LETAIRIS?

LETAIRIS is a prescription medicine to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs.

LETAIRIS can improve your ability to exercise and it can help slow down the worsening of your physical condition and symptoms.

Who should not take LETAIRIS?

Do not take LETAIRIS if:

- **you are pregnant, plan to become pregnant, or become pregnant during treatment with LETAIRIS. LETAIRIS can cause serious birth defects.** (See “What is the most important information I should know about LETAIRIS?”) Serious birth defects from LETAIRIS happen early in pregnancy.
- **your blood tests show possible liver injury.**

Tell your doctor about all your medical conditions and all the medicines you take including prescription and nonprescription medicines. LETAIRIS and other medicines may affect each other causing side effects. Do not start any new medicines until you check with your doctor.

LETAIRIS has not been studied in children.

How should I take LETAIRIS?

LETAIRIS will be mailed to you by a specialty pharmacy. Your doctor will give you complete details.

- Take LETAIRIS exactly as your doctor tells you. Do not stop taking LETAIRIS unless your doctor tells you.
- You can take LETAIRIS with or without food.
- Do not split, crush or chew LETAIRIS tablets.
- It will be easier to remember to take LETAIRIS if you take it at the same time each day.
- If you take more than your regular dose of LETAIRIS, call your doctor right away.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take two doses at the same time to make up for a missed dose.
- During treatment your doctor will test your blood for signs of side effects to your liver and red blood cells.

What should I avoid while taking LETAIRIS?

- **Do not get pregnant** while taking LETAIRIS. (See the serious birth defects section of “What is the most important information I should know about LETAIRIS?”) If you miss a menstrual period, or think you might be pregnant, call your doctor right away.
- **Breastfeeding is not recommended** while taking LETAIRIS. It is not known if LETAIRIS can pass through your milk and harm your baby.

What are the possible side effects of LETAIRIS?

Serious side effects of LETAIRIS include:

- **Possible liver injury.** (See “What is the most important information I should know about LETAIRIS?”) Call your doctor right away if you have any of these symptoms of liver problems: loss of appetite, nausea, vomiting, fever, unusual tiredness, abdominal (stomach area) pain, yellowing of the skin or the whites of your eyes (jaundice), dark urine, or itching.
- **Serious birth defects.** (See “What is the most important information I should know about LETAIRIS?”)
- **Swelling all over the body** (fluid retention) can happen within weeks after starting LETAIRIS. Tell your doctor right away if you have any unusual weight gain, tiredness, or trouble breathing while taking LETAIRIS. These may be symptoms of a serious health problem. You may need to be treated with medicine or need to go to the hospital.
- **Sperm count reduction.** Reduced sperm counts have been observed in some men taking a drug similar to LETAIRIS, an effect which might impair their ability to father a child. Tell your doctor if remaining fertile is important to you.

The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of hands, legs, ankles, and feet (peripheral edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)
- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache
- Allergic reactions (rash, swelling of the face, lips, mouth, tongue, or throat which may cause difficulty in swallowing or breathing) have been reported infrequently

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of LETAIRIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.



Letairis[®]
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How should I store LETAIRIS?

Store LETAIRIS at 59°F to 86°F (15°C to 30°C), in the package it comes in.

Keep LETAIRIS and all medication out of the reach of children.

General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LETAIRIS for a condition for which it was not prescribed. Do not give LETAIRIS to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LETAIRIS. If you would like more information, ask your doctor. You can ask your doctor or pharmacist for information about LETAIRIS that is written for healthcare professionals.

For more information call 1-866-664-LEAP (5327) or visit www.letairis.com or www.gilead.com.

What are the ingredients in LETAIRIS?

Active ingredient: ambrisentan

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.

Questions to ask your doctor

“What can I expect from LETAIRIS treatment?”

“What are the risks and side effects I should know about?”

“What special instructions are there for taking LETAIRIS?”

“Are there any medicines I cannot take while taking LETAIRIS?”

WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations $>3x$ ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations $>3x$ ULN has been accompanied by bilirubin elevations $>2x$ ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. LETAIRIS should generally be avoided in patients with elevated aminotransferases ($>3x$ ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $>2x$ ULN, treatment should be stopped. There is no experience with the re-introduction of LETAIRIS in these circumstances.

CONTRAINDICATION: PREGNANCY

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

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

Please visit www.letairis.com or www.gilead.com for more information.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.



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

Printed on recycled paper.

The Letairis logo features a stylized orange and yellow wave above the word "Letairis" in a large, purple, serif font. Below "Letairis" is the word "ambrisentan" in a smaller, purple, sans-serif font. At the bottom, the text "5 mg and 10 mg Tablets" is written in a small, purple, sans-serif font.

Ongoing Education Program

Gilead Sciences, Inc. is providing you with the most up-to-date LETAIRIS Education and Access Program (LEAP) materials to support your understanding of the program and the risks of LETAIRIS therapy. The materials provided may reflect updates to the LEAP program, program materials, or the full prescribing information (PI) for LETAIRIS.

Enclosed you will find:

- LEAP Prescriber Enrollment Guide
- LEAP Patient Enrollment Guide
- LETAIRIS Therapy: What You Need to Know Brochure
- LETAIRIS PI and Patient Medication Guide

As a LETAIRIS prescriber, it is important that you review the enclosed materials.

Prescriber Information

First Name _____ Middle Initial _____ Last Name _____ Suffix _____
Specialty _____ Name of Facility _____ Office Contact _____
Address _____ City _____ State _____ ZIP _____
E-mail _____ Phone (____) _____ Fax (____) _____
State License # _____ NPI # _____ DEA # _____

Prescriber Agreement

By signing below, you acknowledge that you have received the most recent LEAP materials, and that you understand the risks of LETAIRIS treatment and your obligation as a LETAIRIS prescriber to educate your patients about these risks, counsel them on risk reduction, monitor them appropriately, and report adverse events to LEAP, as described in the LEAP materials.

Prescriber Signature _____ **Date** _____

If you have any questions, please call 1-866-664-LEAP (5327).

Please visit www.letairis.com or www.gilead.com for more information.

LEAP Ongoing Education

Education and A

Instructions

To enroll a patient in LEAP, please complete and fax this form to LEAP at **1-888-882-4035**.

Step 1: Check the box that indicates the type of enrollment.

Step 2: Check the box that indicates preferred specialty pharmacy (SP).

– LEAP makes every effort to use your selected SP. Patients will be redirected with consent only if coverage restrictions apply, or if a lower co-pay is identified.

Step 3: Complete Patient Information section, including preferred contact.

– It is important that your patient provides the best contact number. SP cannot ship LETAIRIS monthly without contacting patient to verify completion of testing and shipping address.

Step 4:

SIGN & DATE

Step 5:

SIGN & DATE

Step 6: Complete Prescriber Information section.

Step 7: Complete Prescription section, including completion of pretherapy testing and Statement of Medical Necessity.

Step 8:

SIGN & DATE

Step 9: Obtain copies of patient insurance information and fax to LEAP at **1-888-882-4035**.

LETAIRIS Education and Access Program (LEAP) Patient Enrollment and Consent Form

Initial Enrollment Re-enrollment Benefits Investigation Only

Select a preferred specialty pharmacy:

Accredo Aetna Specialty Pharmacy CVS Caremark CIGNA Tel-Drug CuraScript Fairview Specialty Pharmacy
 Kaiser Specialty Pharmacy (CA residents only) Walgreens Specialty Pharmacy PrecisionRx Specialty Solutions WellCare Specialty Pharmacy

Patient Information (PLEASE PRINT)

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ / ____ / ____ Gender: M F Preferred Time to Contact: Day Evening

Preferred Phone: (____) _____ Alternate Phone: (____) _____ E-mail: _____

Alternate Contact Name: _____ Phone: (____) _____ Relationship: _____

FAX ALL PATIENT INSURANCE INFORMATION, INCLUDING DRUG BENEFIT CARDS, TO: 1-888-882-4035.

I authorize my healthcare providers and health plans to disclose personal and medical information about me to Gilead and its agents and contractors ("Gilead") and I authorize Gilead to use and disclose this information to: 1) establish my benefit eligibility; 2) communicate with my healthcare providers and health plans about my medical care; 3) provide support services, including facilitating the provision of Letairis® (ambrisentan) to me; and to evaluate the effectiveness of Gilead's education programs. I agree that using the contact information I provide, Gilead may get in touch with me for reasons related to the LEAP program and may leave messages for me that disclose that I take LETAIRIS.

I understand that once my health information has been disclosed to Gilead, privacy laws may no longer restrict its use or disclosure; however, Gilead agrees to protect my information by using and disclosing it only for the purposes described above or as required by law. I further understand I may refuse to sign this authorization and that if I refuse, my eligibility for health plan benefits and treatment by my doctor will not change, but I will not have access to the LETAIRIS support services described herein. I may also cancel this authorization in the future by notifying Gilead in writing and submitting it by fax to 1-888-882-4035 or by calling 1-866-664-LEAP (5327). If I cancel, Gilead will cease using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in LEAP. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

Patient/Guardian Signature: _____ **Date:** _____

By signing below, I acknowledge that I have read the patient Medication Guide and patient education brochure and that I have been informed about the risks of LETAIRIS, including the risks of liver injury, serious birth defects, low red blood cell count, and low sperm count. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risks of LETAIRIS treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for women who are able to become pregnant) and, if I am a woman who becomes pregnant, to obtain information about my pregnancy.

Patient/Guardian Signature: _____ **Date:** _____

Prescriber Information (PLEASE PRINT) Office Contact: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (____) _____ Fax: (____) _____ NPI #: _____ DEA #: _____

Prescription: LETAIRIS: 5 mg tablets (30 tablets) Refills: _____ 10 mg tablets (30 tablets) Refills: _____

Instructions: _____

Ship to: Patient Home (address listed above) Prescriber Office (address listed above) Other: (please indicate below)

Name: _____ Address: _____

City: _____ State: _____ ZIP: _____ Phone: (____) _____

For all patients, please indicate whether pre-LETAIRIS liver function test has been completed: Yes No

For female patients only, please indicate whether this patient is of childbearing potential: Yes No

(Please note that female patients who have had a tubal sterilization are considered to be of childbearing potential.)

– If yes, has a negative pre-LETAIRIS pregnancy test been confirmed? Yes No

Statement of Medical Necessity (This is for insurance purposes only, not to suggest approved uses or indications.)

Diagnosis: Pulmonary Arterial Hypertension (Please select one category below)

Familial (ICD 416.0) Idiopathic (ICD 416.0) Scleroderma (ICD 710.1) HIV (ICD 042 _____) Lupus (ICD 710.0)

Portal Hypertension (ICD 572.3) Congenital Heart Defects (ICD 745. _____) Other: _____ (ICD _____)

I certify that I am prescribing LETAIRIS for a medically appropriate use in the treatment of pulmonary arterial hypertension, as described in the LETAIRIS full prescribing information. I have reviewed the Medication Guide and patient education brochure with the patient and have counseled them on the risks of LETAIRIS, including hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I commit to ordering and reviewing liver function, pregnancy (if this patient is a female of childbearing potential), and hemoglobin tests in accordance with the LETAIRIS full prescribing information.

Prescriber Signature: _____ **Date:** _____

 **GILEAD** Please visit www.letairis.com or www.gilead.com or call **1-866-664-LEAP (5327)** for more information.

LETAIRIS Education and Access Program (LEAP) Instructions

LEAP is a program to help prescribers and patients learn about the risks of Letairis® (ambrisentan), including the serious risks of liver injury and birth defects. Because of the risk of liver injury, and in an effort to make the chance of fetal exposure to LETAIRIS as small as possible, LETAIRIS may only be prescribed through the LEAP program.

Please complete the following steps prior to faxing the patient enrollment form.

Step 1: Check the box that indicates if this patient is a new enrollment, re-enrollment, or benefits investigation only

Step 2: Check the box that indicates the patient's preferred specialty pharmacy

Step 3: Complete Patient Information section, including the best method for LEAP to contact your patient

Step 4: Obtain patient signature. Two signatures are required for HIPAA release and to confirm that the patient has read the LETAIRIS patient Medication Guide and has been informed of the risks of LETAIRIS

Step 5: Obtain second patient signature

Step 6: Complete Prescriber Information section, including office contact for additional questions regarding this application

Step 7: Complete Prescription section

Step 8: Prescriber must sign the form

Step 9: Fax completed form and copies of all relevant insurance information to **LEAP** at **1-888-882-4035**

Please visit www.letairis.com or www.gilead.com or call **1-866-664-LEAP (5327)** for more information.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.



LETAIRIS Education and Access Program (LEAP) and LabSync Patient Enrollment and Consent Form

Initial Enrollment
 Re-enrollment
 Benefits Investigation Only
 Enroll Patient in LabSync: Yes No

Select a preferred specialty pharmacy:

- Accredo
 Aetna Specialty Pharmacy
 CVS Caremark
 CIGNA Tel-Drug
 CuraScript
 Fairview Specialty Pharmacy
 Kaiser Specialty Pharmacy (CA residents only)
 PrecisionRx Specialty Solutions
 Walgreens Specialty Pharmacy
 WellCare Specialty Pharmacy

Patient Information (PLEASE PRINT)

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ / ____ / ____ Gender: M F Preferred Time to Contact: Day Evening

Preferred Phone: (____) _____ Alternate Phone: (____) _____ E-mail: _____

Alternate Contact Name: _____ Phone: (____) _____ Relationship: _____

FAX ALL PATIENT INSURANCE INFORMATION, INCLUDING DRUG BENEFIT CARDS, TO: 1-888-882-4035.

I authorize my healthcare providers and health plans to disclose personal and medical information about me to Gilead and its agents and contractors ("Gilead") and I authorize Gilead to use and disclose this information to: 1) establish my benefit eligibility, including benefit eligibility for laboratory services; 2) communicate with my healthcare providers and health plans about my medical care; 3) provide support services, including facilitating the provision of Letairis® (ambrisentan) to me and facilitating laboratory testing on my behalf; and 4) evaluate the safety and overall effectiveness of Gilead's education program, the LEAP and LabSync programs, as well as the safety and efficacy of LETAIRIS. I agree that using the contact information I provide, Gilead may get in touch with me for reasons related to the LEAP and LabSync programs and may leave messages for me that disclose that I take LETAIRIS. Additionally, I understand that I may choose not to participate in LabSync, but I am still eligible to participate in LEAP.

I understand that once my health information has been disclosed to Gilead, privacy laws may no longer restrict its use or disclosure; however, Gilead agrees to protect my information by using and disclosing it only for the purposes described above or as required by law. I further understand I may refuse to sign this authorization and that if I refuse, my eligibility for health plan benefits and treatment by my doctor will not change, but I will not have access to the LETAIRIS support services described herein. I may also cancel this authorization in the future by notifying Gilead in writing and submitting it by fax to 1-888-882-4035 or by calling 1-866-664-LEAP (5327). If I cancel, Gilead will cease using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in LEAP. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

Patient/Guardian Signature: _____ **Date:** _____

By signing below, I acknowledge that I have read the patient Medication Guide and patient education brochure and that I have been informed about the risks of LETAIRIS, including the risks of liver injury, serious birth defects, low red blood cell count, and low sperm count. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risks of LETAIRIS treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for women who are able to become pregnant) and, if I am a woman who becomes pregnant, to obtain information about my pregnancy.

Patient/Guardian Signature: _____ **Date:** _____

Prescriber Information (PLEASE PRINT) Office Contact and E-mail Address: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (____) _____ Fax: (____) _____ NPI #: _____ DEA #: _____

Prescription: LETAIRIS: 5 mg tablets (30 tablets) Refills: _____ 10 mg tablets (30 tablets) Refills: _____

Instructions: _____

Ship to: Patient Home (address listed above) Prescriber Office (address listed above) Other: (please indicate below)

Name: _____ Address: _____

City: _____ State: _____ ZIP: _____ Phone: (____) _____

For all patients, please indicate whether pre-LETAIRIS liver function test has been completed: Yes No

For female patients only, please indicate whether this patient is of childbearing potential: Yes No

(Please note that female patients who have had a tubal sterilization are considered to be of childbearing potential.)

- If yes, has a negative pre-LETAIRIS pregnancy test been confirmed? Yes No

Statement of Medical Necessity (This is for insurance purposes only, not to suggest approved uses or indications.)

Diagnosis: Pulmonary Arterial Hypertension (Please select one category below)

Familial (ICD 416.0)
 Idiopathic (ICD 416.0)
 Scleroderma (ICD 710.1)
 HIV (ICD 042 _____)
 Lupus (ICD 710.0)

Portal Hypertension (ICD 572.3)
 Congenital Heart Defects (ICD 745. _____)
 Other: _____ (ICD _____)

I certify that I am prescribing LETAIRIS for a medically appropriate use in the treatment of pulmonary arterial hypertension, as described in the LETAIRIS full prescribing information. I have reviewed the Medication Guide and patient education brochure with the patient and have counseled them on the risks of LETAIRIS, including hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I commit to ordering and reviewing liver function, pregnancy (if this patient is a female of childbearing potential), and hemoglobin tests in accordance with the LETAIRIS full prescribing information. I authorize LabSync to order laboratory tests and receive laboratory results on my behalf for patients enrolled in LEAP and LabSync.

Prescriber Signature: _____ **Date:** _____

LETAIRIS Education and Access Program (LEAP) Instructions

LEAP is a program to help prescribers and patients learn about the risks of Letairis® (ambrisentan), including the serious risks of liver injury and birth defects. Because of the risk of liver injury, and in an effort to make the chance of fetal exposure to LETAIRIS as small as possible, LETAIRIS may only be prescribed through the LEAP program.

Please complete the following steps prior to faxing the patient enrollment form.

Step 1: Check the box that indicates if this patient is a new enrollment, re-enrollment, or benefits investigation only

Step 2: Check “Yes” or “No” to indicate whether patient will participate in LabSync

Step 3: Check the box that indicates the patient’s preferred specialty pharmacy

Step 4: Complete Patient Information section, including the best method for LEAP to contact your patient

Step 5: Obtain patient signature. Two signatures are required for HIPAA release and to confirm that the patient has read the LETAIRIS patient Medication Guide and has been informed of the risks of LETAIRIS

Step 6: Obtain second patient signature

Step 7: Complete Prescriber Information section, including office contact for additional questions regarding this application

Step 8: Complete Prescription section

Step 9: Prescriber must sign the form

Step 10: Fax completed form and copies of all relevant insurance information to **LEAP** at **1-888-882-4035**

Please visit www.letairis.com or www.gilead.com or call **1-866-664-LEAP (5327)** for more information.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.



FOR V.A. USE ONLY

LETAIRIS Education and Access Program (LEAP) Patient Enrollment and Consent Form

Initial Enrollment Re-enrollment

Specialty pharmacy: Accredo

Patient Information (PLEASE PRINT)

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ / ____ / ____ Gender: M F Preferred Time to Contact: Day Evening

Preferred Phone: (_____) _____ Alternate Phone: (_____) _____ E-mail: _____

Alternate Contact Name: _____ Phone: (_____) _____ Relationship: _____

FAX ALL PATIENT INSURANCE INFORMATION, INCLUDING DRUG BENEFIT CARDS, TO: 1-888-882-4035.

I authorize Veterans Health Care Administration ("VA"), my specialty pharmacy or pharmacies, and my health plans to disclose personal and medical information about me to LEAP, which is run by Gilead and its agents and contractors ("LEAP"). I authorize LEAP to use and disclose this information to (1) establish my eligibility for benefits; (2) communicate with my healthcare providers and health plans about my medical care; and (3) provide Letairis® (ambrisentan) support services, including facilitating the provision of LETAIRIS to me; and evaluate the effectiveness of Gilead's education programs. I agree that using the contact information I provide, LEAP may get in touch with me for reasons related to LEAP and may leave messages for me that disclose that I take LETAIRIS. I understand that once my health information has been disclosed to LEAP, privacy laws may no longer restrict its use or disclosure; however, LEAP agrees to use and disclose the information only as permitted in this authorization or as required by law.

I further understand I may refuse to sign this authorization and that if I refuse, my eligibility for health plan benefits and treatment by my doctor will not change, but I will not be eligible to receive LETAIRIS since, as a result of not signing, I will not have access to the FDA-required LETAIRIS support services described herein. I may also cancel this authorization in the future by notifying LEAP in writing and submitting it by fax to 1-888-882-4035 or by calling 1-866-664-LEAP (5327). If I cancel this authorization, LEAP will cease using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in LEAP. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

Patient/Guardian Signature: _____ **Date:** _____

By signing below, I acknowledge that I have read the patient Medication Guide and patient education brochure and that I have been informed about the risks of LETAIRIS, including the risks of liver injury, serious birth defects, low red blood cell count, and low sperm count. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risks of LETAIRIS treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for women who are able to become pregnant) and, if I am a woman who becomes pregnant, to obtain information about my pregnancy.

Patient/Guardian Signature: _____ **Date:** _____

Prescriber Information (PLEASE PRINT) Office Contact: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (_____) _____ Fax: (_____) _____ NPI #: _____ DEA #: _____

Prescription: LETAIRIS: 5 mg tablets (30 tablets) Refills: _____ 10 mg tablets (30 tablets) Refills: _____
Instructions: _____
Ship to: Patient Home (address listed above) Prescriber Office (address listed above) Other: (please indicate below)
Name: _____ Address: _____
City: _____ State: _____ ZIP: _____ Phone: (_____) _____
For all patients, please indicate whether a pre-LETAIRIS liver function test has been completed: Yes No
For female patients only, please indicate whether patient is of childbearing potential: Yes No
(Please note that female patients who have had a tubal sterilization are considered to be of childbearing potential.)
- If yes, has a negative pre-LETAIRIS pregnancy test been confirmed? Yes No

Statement of Medical Necessity (This is not to suggest approved uses or indications.)

Diagnosis: Pulmonary Arterial Hypertension (Please select one category below)

- Familial (ICD 416.0) Idiopathic (ICD 416.0) Scleroderma (ICD 710.1) HIV (ICD 042 _____) Lupus (ICD 710.0)
- Portal Hypertension (ICD 572.3) Congenital Heart Defects (ICD 745. _____) Other: _____ (ICD _____)

I certify that I am prescribing LETAIRIS for a medically appropriate use in the treatment of pulmonary arterial hypertension, as described in the LETAIRIS full prescribing information. I have reviewed the Medication Guide and patient education brochure with the patient and have counseled them on the risks of LETAIRIS, including hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I commit to ordering and reviewing liver function, pregnancy (if this patient is a female of childbearing potential), and hemoglobin tests in accordance with the LETAIRIS full prescribing information.

Prescriber Signature: _____ **Date:** _____

LETAIRIS Education and Access Program (LEAP) Instructions

LEAP is a program to help prescribers and patients learn about the risks of Letairis® (ambrisentan), including the serious risks of liver injury and birth defects. Because of the risk of liver injury, and in an effort to make the chance of fetal exposure to LETAIRIS as small as possible, LETAIRIS may only be prescribed through the LEAP program.

Please complete the following steps prior to faxing the patient enrollment form.

Step 2: Check the box that indicates the patient's preferred specialty pharmacy
Step 4: Obtain patient signature. Two signatures are required for HIPAA release and to confirm that the patient has read the LETAIRIS patient Medication Guide and has been informed of the risks of LETAIRIS
Step 6: Complete Prescriber Information section, including office contact for additional questions regarding this application
Step 8: Prescriber must sign the form

Please visit www.letairis.com or www.gilead.com or call **1-866-664-LEAP (5327)** for more information.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.

FOR V.A. USE ONLY

LETAIRIS Education and Access Program (LEAP) Patient Enrollment and Consent Form

Initial Enrollment Re-enrollment

Select a preferred specialty pharmacy: Accredo CVS Caremark

Patient Information (PLEASE PRINT)

First Name: _____ Middle Initial: _____ Last Name: _____

Address: _____ City: _____ State: _____ ZIP: _____

Birthdate: ____ / ____ / ____ Gender: M F Preferred Time to Contact: Day Evening

Preferred Phone: (____) _____ Alternate Phone: (____) _____ E-mail: _____

Alternate Contact Name: _____ Phone: (____) _____ Relationship: _____

FAX ALL PATIENT INSURANCE INFORMATION, INCLUDING DRUG BENEFIT CARDS, TO: 1-888-882-4035.

I authorize Veterans Health Care Administration ("VA"), my specialty pharmacy or pharmacies, and my health plans to disclose personal and medical information about me to LEAP, which is run by Gilead and its agents and contractors ("LEAP"). I authorize LEAP to use and disclose this information to (1) establish my eligibility for benefits; (2) communicate with my healthcare providers and health plans about my medical care; and (3) provide Letairis® (ambrisentan) support services, including facilitating the provision of LETAIRIS to me; and evaluate the effectiveness of Gilead's education programs. I agree that using the contact information I provide, LEAP may get in touch with me for reasons related to LEAP and may leave messages for me that disclose that I take LETAIRIS. I understand that once my health information has been disclosed to LEAP, privacy laws may no longer restrict its use or disclosure; however, LEAP agrees to use and disclose the information only as permitted in this authorization or as required by law.

I further understand I may refuse to sign this authorization and that if I refuse, my eligibility for health plan benefits and treatment by my doctor will not change, but I will not be eligible to receive LETAIRIS since, as a result of not signing, I will not have access to the FDA-required LETAIRIS support services described herein. I may also cancel this authorization in the future by notifying LEAP in writing and submitting it by fax to 1-888-882-4035 or by calling 1-866-664-LEAP (5327). If I cancel this authorization, LEAP will cease using or disclosing my information for the purposes listed above, except as required by law or as necessary for the orderly termination of my participation in LEAP. I am entitled to a copy of this signed authorization, which expires 10 years from the date it is signed by me.

Patient/Guardian Signature: _____ **Date:** _____

By signing below, I acknowledge that I have read the patient Medication Guide and patient education brochure and that I have been informed about the risks of LETAIRIS, including the risks of liver injury, serious birth defects, low red blood cell count, and low sperm count. I acknowledge that I will be contacted by Gilead and/or its agents and contractors to receive counseling on the risks of LETAIRIS treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for women who are able to become pregnant) and, if I am a woman who becomes pregnant, to obtain information about my pregnancy.

Patient/Guardian Signature: _____ **Date:** _____

Prescriber Information (PLEASE PRINT) Office Contact: _____

First Name: _____ Last Name: _____ State License #: _____

Address: _____ City: _____ State: _____ ZIP: _____

Phone: (____) _____ Fax: (____) _____ NPI #: _____ DEA #: _____

Prescription: LETAIRIS: 5 mg tablets (30 tablets) Refills: _____ 10 mg tablets (30 tablets) Refills: _____

Instructions: _____

Ship to: Patient Home (address listed above) Prescriber Office (address listed above) Other: (please indicate below)

Name: _____ Address: _____

City: _____ State: _____ ZIP: _____ Phone: (____) _____

For all patients, please indicate whether a pre-LETAIRIS liver function test has been completed: Yes No

For female patients only, please indicate whether patient is of childbearing potential: Yes No

(Please note that female patients who have had a tubal sterilization are considered to be of childbearing potential.)

- If yes, has a negative pre-LETAIRIS pregnancy test been confirmed? Yes No

Statement of Medical Necessity (This is not to suggest approved uses or indications.)

Diagnosis: Pulmonary Arterial Hypertension (Please select one category below)

Familial (ICD 416.0) Idiopathic (ICD 416.0) Scleroderma (ICD 710.1) HIV (ICD 042 _____) Lupus (ICD 710.0)

Portal Hypertension (ICD 572.3) Congenital Heart Defects (ICD 745. _____) Other: _____ (ICD _____)

I certify that I am prescribing LETAIRIS for a medically appropriate use in the treatment of pulmonary arterial hypertension, as described in the LETAIRIS full prescribing information. I have reviewed the Medication Guide and patient education brochure with the patient and have counseled them on the risks of LETAIRIS, including hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, and the potential risk of reduced male fertility. I commit to ordering and reviewing liver function, pregnancy (if this patient is a female of childbearing potential), and hemoglobin tests in accordance with the LETAIRIS full prescribing information.

Prescriber Signature: _____ **Date:** _____

LETAIRIS Education and Access Program (LEAP) Instructions

LEAP is a program to help prescribers and patients learn about the risks of Letairis® (ambrisentan), including the serious risks of liver injury and birth defects. Because of the risk of liver injury, and in an effort to make the chance of fetal exposure to LETAIRIS as small as possible, LETAIRIS may only be prescribed through the LEAP program.

Please complete the following steps prior to faxing the patient enrollment form.

Step 1: Check the box that indicates if this patient is a new enrollment or re-enrollment
Step 2: Check the box that indicates the patient's preferred specialty pharmacy
Step 3: Complete Patient Information section, including the best method for LEAP to contact your patient
Step 4: Obtain patient signature. Two signatures are required for HIPAA release and to confirm that the patient has read the LETAIRIS patient Medication Guide and has been informed of the risks of LETAIRIS
Step 5: Obtain second patient signature
Step 6: Complete Prescriber Information section, including office contact for additional questions regarding this application
Step 7: Complete Prescription section
Step 8: Prescriber must sign the form
Step 9: Fax completed form and copies of all relevant insurance information to LEAP at 1-888-882-4035

Please visit www.letairis.com or www.gilead.com or call **1-866-664-LEAP (5327)** for more information.

Please see accompanying patient Medication Guide and full prescribing information, including **boxed WARNINGS**.