

## 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 thereafter by the use of two reliable methods of contraception (2.2)

### 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 child-bearing potential only after a negative pregnancy test and treat only women who are using two reliable methods of contraception unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted. Obtain monthly pregnancy tests (2.2).
- Not recommended in patients with moderate or severe hepatic impairment (2.3)

### DOSAGE FORMS AND STRENGTHS

- 5 mg and 10mg 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).
- Mild to moderate peripheral edema (5.3)
- Use caution when LETAIRIS is co-administered with cyclosporine A (5.4 and 7).
- Use caution when LETAIRIS is co-administered with strong CYP3A and 2C19 inhibitors (5.5 and 7).

### ADVERSE REACTIONS

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

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

### DRUG INTERACTIONS

- No significant interactions of LETAIRIS with warfarin or sildenafil have been observed (7).
- 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), CYP3A4, and CYP2C19 inhibitors, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) would be expected (7).

### USE IN SPECIFIC POPULATIONS

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

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

Revised: 06/2007

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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 thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNG 20 IUD inserted, in which case no other 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, Prescribing and Distribution Program for LETAIRIS*].

## 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 reliable methods of contraception unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted. In those cases, no other contraception is needed. Pregnancy tests should be obtained monthly in women of childbearing potential taking LETAIRIS [see *Contraindications (4.1)*].

### 2.3 Pre-existing Hepatic Impairment

LETAIRIS is not recommended in patients with moderate or severe hepatic impairment [see *Special Populations (8.7)*]. Use caution in patients with mild hepatic impairment.

## 3 DOSAGE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

### 4.1 Pregnancy Category X

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

LETAIRIS is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of two reliable methods of contraception [see *Dosage and Administration (2.2)*].

## 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.

Hemoglobin must be measured prior to initiation of LETAIRIS and should be measured at one month and periodically thereafter. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, discontinuation of treatment should be considered.

### **5.3 Peripheral Edema**

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. If clinically significant peripheral edema develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as heart failure, and the possible need for specific treatment.

### **5.4 Co-administration of LETAIRIS and Cyclosporine A**

Cyclosporine is a strong inhibitor of P-glycoprotein (P-gp), Organic Anion Transport Protein (OATP), and CYP3A4. *In vitro* data indicate ambrisentan is a substrate of P-gp, OATP and CYP3A. Therefore, use caution when LETAIRIS is co-administered with cyclosporine A because cyclosporine A may cause increased exposure to LETAIRIS [see *Drug Interactions (7)*].

### **5.5 Co-administration of LETAIRIS and Strong CYP3A and 2C19 Inhibitors**

Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) and CYP2C19-inhibitors (e.g., omeprazole) [see *Drug Interactions (7)*].

### **5.6 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 6 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 two different forms of contraception including at least one primary form during LETAIRIS treatment and for one month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed [see *Boxed Warning, Contraindication (4.1)*].

Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone, i.e. without a secondary form of contraception, as can tubal sterilization.

Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.

- 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

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 ≥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).

## 7 DRUG INTERACTIONS

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A4, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of Organic Anion Transport Protein (OATP). *In vitro* studies show ambrisentan is a substrate but not an inhibitor of P-gp.

The drug interaction potential of ambrisentan is not well characterized because *in vivo* drug interaction studies were not conducted with the following types of drugs: strong inhibitors of CYP3A4 (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin), and CYP2C19 (omeprazole), strong inducers of CYP3A and 2C19 (rifampin), strong inhibitors of the transporters P-gp (cyclosporine A) and OATP (cyclosporine A, rifampin); and inducers of CYPs, UGTs and P-gp (rifampin). The impact of co-administration of such drugs on ambrisentan exposure is therefore unknown.

### **7.1 Cyclosporine A**

Use caution when LETAIRIS is co-administered with cyclosporine A (see Warnings and Precautions 5.4).

### **7.2 Strong CYP3A or 2C19 Inhibitors**

Use caution when LETAIRIS is co-administered with strong CYP3A-inhibitors (e.g., ketoconazole) or CYP2C19-inhibitors (e.g., omeprazole) [*see Warnings and Precautions (5.5)*].

### **7.3 Inducers of P-gp, CYPs, and UGTs**

Use caution when LETAIRIS is co-administered with inducers of P-gp, CYPs, and UGTs.

### **7.4 Warfarin**

In healthy volunteers receiving warfarin, daily doses of LETAIRIS (10 mg once daily) did not have a clinically significant effect on prothrombin time (PT), International Normalized Ratio (INR), or the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate).

In patients with PAH receiving warfarin-type anticoagulants, concomitant administration of LETAIRIS did not result in a clinically relevant change in PT, INR or anticoagulant dose. Therefore, no dose-adjustments for warfarin or LETAIRIS are required when co-administered.

### **7.5 Sildenafil**

In healthy volunteers receiving a single dose of sildenafil (20 mg), daily doses of LETAIRIS (10 mg once daily) did not have a clinically relevant effect on the pharmacokinetics of sildenafil or the active metabolite, n-desmethyl sildenafil. Similarly, daily doses of sildenafil (20 mg tid) did not have a clinically relevant effect on the pharmacokinetics of a single dose of LETAIRIS (10 mg). Therefore, no dose-adjustments for sildenafil or LETAIRIS are required when co-administered.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

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

### 8.5 Geriatric Use

In the two placebo-controlled clinical studies of LETAIRIS, 21% of patients were ≥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. Use caution when administering LETAIRIS to patients with mild pre-existing impaired liver function who may require reduced doses of LETAIRIS [see *Dosage and Administration* (2.3)].

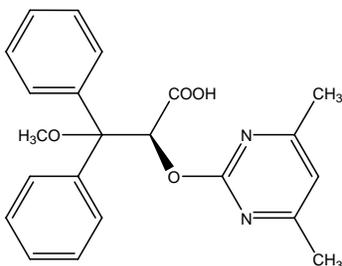
## 10 OVERDOSAGE

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

**Figure 1 Ambrisentan Structural Formula**



Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pK<sub>a</sub> 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<sub>A</sub> and ET<sub>B</sub>, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ET<sub>A</sub> are vasoconstriction and cell proliferation, while the predominant actions of ET<sub>B</sub> 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 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. Based on *in vitro* data, interactions with strong inhibitors of P glycoprotein (P-gp), the Organic Anion Transport Protein (OATP), CYP3A4, CYP2C19, and uridine 5' diphosphate glucuronosyltransferases (UGTs) are possible [see *Drug Interactions (7)*]. 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of up to two years duration were conducted at starting doses of 10, 30, and 60 mg/kg/day in rats (8 to 48 times the maximum recommended human dose [MRHD] on a  $mg/m^2$  basis) and at 50, 150 and 250 mg/kg/day in mice (28 to 140 times the MRHD). In the rat study, the high and mid-dose male and female groups had their doses lowered to 40 and 20 mg/kg/day, respectively, in week 51 because of effects on survival. The high dose males and females were taken off drug completely in weeks 69 and 93, respectively. The only evidence of ambrisentan-related carcinogenicity was a positive trend in male rats, for the combined incidence of benign basal cell tumor and basal cell carcinoma of skin/subcutis in the mid-dose group (high-dose group excluded from analysis), and the occurrence of mammary fibroadenomas in males in the high-dose group. In the mouse study, high dose male and female groups had their doses lowered to 150 mg/kg/day in week 39 and were

taken off drug completely in week 96 (males) or week 76 (females). In mice, ambrisentan was not associated with excess tumors in any dosed group.

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

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of endothelin receptor antagonists in rodents. Testicular tubular degeneration was observed in rats treated with ambrisentan for two years at doses  $\geq 10$  mg/kg/day (8-fold MRHD). Increased incidences of testicular findings were also observed in mice treated for two years at doses  $\geq 50$  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  $\geq 10$  mg/kg/day, observations of testicular histopathology in the absence of fertility and sperm effects were also present. There are insufficient data on the effects of ambrisentan or other endothelin receptor antagonists on testicular function in man.

## **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<sup>®</sup> 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.

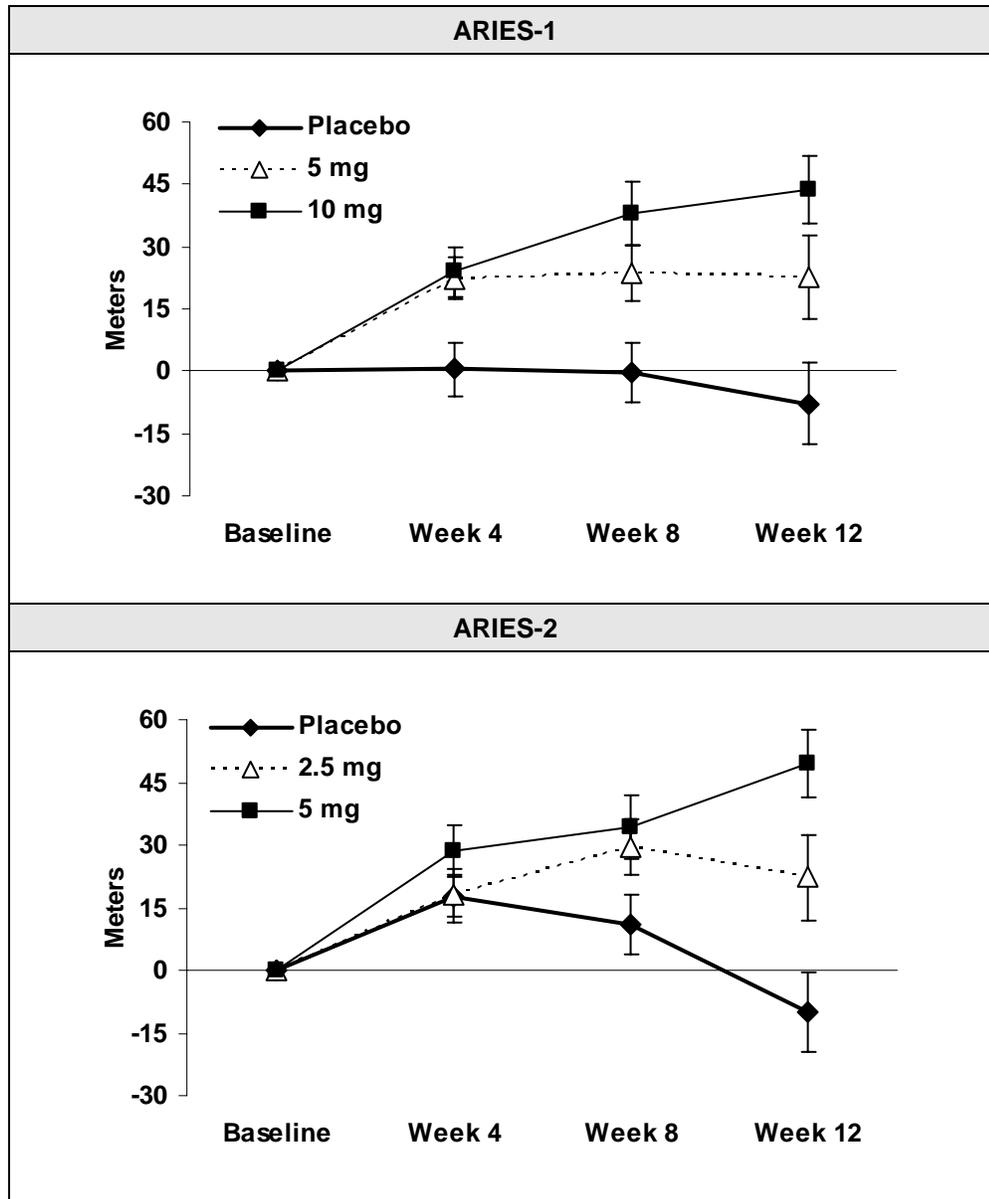
**Table 2** Changes from Baseline in 6-Minute Walk Distance (meters)

	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  $\geq 65$ ) 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

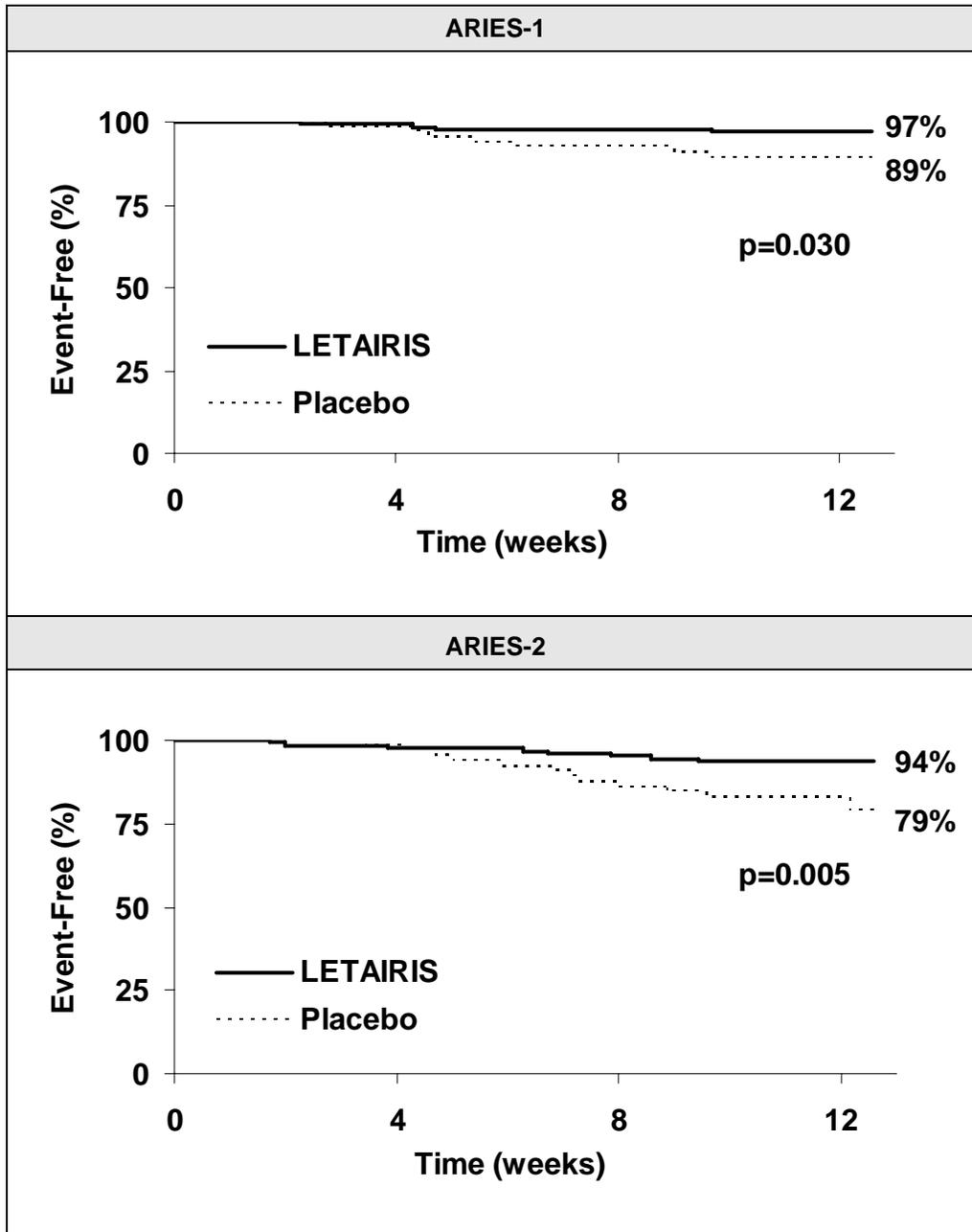
Intention-to-treat population

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](http://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 two different forms of contraception including at least one primary form simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. Primary forms of contraception other than tubal sterilization include hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNG 20 IUD can be used alone, i.e. without a secondary form of contraception, as can tubal sterilization. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant [see *Prescribing and Distribution Program for LETAIRIS (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

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GS22-081-000

**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 different reliable 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, right upper stomach 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?”)
- **Low sperm count.** LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

### The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of legs and ankles (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

## How should I store LETAIRIS?

Store LETAIRIS at less than 86 °F (30 °C), in the package it comes in.

## General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about LETAIRIS, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about LETAIRIS. Your doctor can give you information about LETAIRIS that was written for healthcare professionals. Do not use LETAIRIS

for any condition other than that for which it was prescribed. Do not share LETAIRIS with other people. It may harm them.

Call 1-866-664-LEAP (5327) or visit [www.letairis.com](http://www.letairis.com) or [www.gilead.com](http://www.gilead.com) for more information.

### **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.

This medication guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

June 2007

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GS22-081-000

Carton, Letairis 5 mg, DRAFT  
FILE NAME/PART NO.: 4000412 IC-5414/S



Colors shown may be darker than actual PMS. Please refer to color standards.

DIMENSIONS: 3.0" x 1.0" x 4.5"  
KEYLINE #: D5394A  
BARCODE: UPC-A 61958-0801-2  
DATE: 15 JUNE 2007  
PROOF #: 1



Carton, Letairis 10 mg, DRAFT  
FILE NAME/PART NO.: 4000413 IC-5415/S



Colors shown may be darker than actual PMS. Please refer to color standards.

DIMENSIONS: 3.0" x 1.0" x 4.5"  
KEYLINE #: D5394A  
BARCODE: UPC-A 61958-0802-2  
DATE: 15 JUNE 2007  
PROOF #: 1



**GILEAD SCIENCES, INC.**

**RISK MANAGEMENT PLAN  
LETAIRIS™ (AMBRISENTAN)**

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## 6.0 RISK MINIMIZATION ACTION PLAN

The proposed LETAIRIS RiskMAP focuses on reducing the risks of teratogenicity associated with LETAIRIS treatment by using targeted education and outreach to prescribers and patients and a performance-linked, closed distribution system for dispensing LETAIRIS.

While the key goal of the RiskMAP is to minimize the risks of hepatotoxicity and teratogenicity, other risks and safety concerns, including the risk of decreases in hemoglobin concentration and hematocrit and the potential risk of reduced male fertility, will also be addressed in educational materials and tools for prescribers and patients.

Specific elements of the LETAIRIS RiskMAP include:

- Education of prescribers and patients on the risks of hepatotoxicity and teratogenicity associated with LETAIRIS treatment
- Mandatory enrollment of all prescribers into the RiskMAP program, with written self-attestation (Appendix 2)
- Mandatory enrollment of all patients into the RiskMAP program with consent to release health information, and for female patients of childbearing potential, to be contacted if she becomes pregnant to obtain information about the pregnancy (Appendix 3)
- Mandatory liver function testing and pregnancy testing (for female patients of childbearing potential) prior to initiation of LETAIRIS treatment and monthly during treatment
- Mandatory monthly calls to all patients to obtain confirmation that the required testing was completed
- Mandatory monthly calls to all patients to provide counseling on the RiskMAP program requirements and risks of LETAIRIS treatment
- Distribution of LETAIRIS through a performance-linked, closed distribution system that provides LETAIRIS only to patients enrolled in the RiskMAP program. LETAIRIS will be available only through select Specialty Pharmacies
- Packaging of LETAIRIS in a 30-day supply with a Medication Guide
- Re-enrollment of patients into the RiskMAP program after the first 6 months of treatment and annually thereafter

For the purpose of the RiskMAP Program, a female patient of childbearing potential will be defined as a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

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 - 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.

The LETAIRIS RiskMAP activities will supplement the LETAIRIS labeling and routine pharmacovigilance processes (Section 4.0 of the Risk Management Plan). In addition, there will be an ongoing evaluation of the RiskMAP to provide a continuing and iterative assessment of the effectiveness of the program and of the benefit-risk profile of LETAIRIS.

## **6.1 RiskMAP Goals**

The risk minimization goals of the LETAIRIS RiskMAP are:

- To promote informed benefit-risk decisions regarding the use of LETAIRIS
- To minimize the risk of hepatotoxicity in patients prescribed LETAIRIS
- To minimize the risk of fetal exposure and adverse fetal outcomes in female patients of childbearing potential prescribed LETAIRIS
  - Women who are pregnant must not be prescribed LETAIRIS
  - Women taking LETAIRIS must not become pregnant

## **6.2 RiskMAP Objectives**

### **6.2.1 Objectives for Prescribers**

Physicians who prescribe LETAIRIS must be enrolled in the RiskMAP program and understand the risks associated with LETAIRIS treatment including the risks of hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit and the potential risk of reduced male fertility. Prior to treating any patient with LETAIRIS, prescribers must:

- Review the RiskMAP educational materials (Appendices 1 through 3)
- Enroll as a prescriber and complete a self-attestation form (Appendix 2) indicating agreement to:
  - Read the full prescribing information (PI) and Medication Guide, for LETAIRIS
  - Enroll all patients in the RiskMAP program

- 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, teratogenicity, decreases in hemoglobin and hematocrit and the potential risk of reduced male fertility
- Educate female patients of childbearing potential about the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, no additional contraception is needed.
  - Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD and a partner’s vasectomy. A Copper T 380A IUD or LNG 20 IUD can be used alone, (i.e. without a secondary form of contraception, as can tubal sterilization).
  - Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms and cervical caps
- Order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests (for female patients of childbearing potential) prior to initiation of LETAIRIS treatment and monthly during treatment
- Counsel the patient if the patient is not complying with the required testing or, for female patients of childbearing potential, if she is not using appropriate contraception
- Report any adverse events, including liver injury, and any patient who becomes pregnant during LETAIRIS treatment to Gilead
- Re-enroll patients into the RiskMAP program after the first 6 months of treatment then annually thereafter

Information on enrolled prescribers will be collected in a validated database that captures enrollment data and date of self-attestation; prescribers will be linked to their enrolled patients.

### **6.2.2 Objectives for Patients**

All patients must be enrolled in the RiskMAP program to receive LETAIRIS. In addition, each patient must sign the enrollment form (Appendix 3) indicating they have read the LETAIRIS Medication Guide (Appendix 1) and patient educational materials (Appendix 3) and agree to be contacted, prior to each shipment of LETAIRIS, to obtain confirmation that liver function testing was completed and to be counseled on the requirements of the RiskMAP program and the risks of LETAIRIS.

In addition, each female patient of childbearing potential must:

- Have a pregnancy test before starting LETAIRIS treatment and monthly during LETAIRIS treatment to confirm she is not pregnant
- Agree to be contacted each month to confirm that she completed her pregnancy test

- Use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation. If she has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, no additional contraception is needed.
- Discuss with their prescriber or a healthcare professional with expertise in contraception counseling suitable forms of contraception
- Contact her doctor if she misses a menstrual period or thinks she might be pregnant
- Acknowledge that she will be contacted by the Gilead DSPH Department if she becomes pregnant while on LETAIRIS or within 30 days after treatment discontinuation

Information on enrolled patients will be collected in a validated database that captures enrollment data and self-attestation. The database will link the patient to his/her enrolled prescriber. To protect patient privacy, all patients entered in the database will be assigned a unique identifying number.

### **6.2.3 Objectives for the RiskMAP Coordinating Center**

Gilead will contract an appropriately experienced service organization staffed by technical and healthcare experts to serve as the RiskMAP Coordinating Center for the LETAIRIS RiskMAP.

Specifically, the RiskMAP Coordinating Center must:

- Provide educational materials and tools to enrolled prescribers
- Provide a toll free number that will be appropriately staffed by technical and healthcare professionals to receive calls from prescribers and patients
- Receive and database the prescriber and patient enrollment forms
- Call patients every month to obtain confirmation that liver function testing and pregnancy testing was completed

For patients who respond affirmatively that they completed the required testing, provide an authorization number to the Specialty Pharmacy allowing the Specialty Pharmacy to dispense a 30-day supply of LETAIRIS

For patients who are unable to respond affirmatively that they completed the required testing or who cannot be reached:

- Remind the patient, if possible, of the importance of completing the required testing and instruct the patient to call his/her prescriber to schedule the test(s)
- Call the patient's prescriber to remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for female patients of childbearing potential)
- Ask the prescriber whether or not he/she authorizes the refill of LETAIRIS

- If authorized by the prescriber, provide an authorization number to the Specialty Pharmacy allowing the Specialty Pharmacy to dispense a 30-day supply of LETAIRIS
- Notify Gilead DSPH of any reports of adverse events, including liver injury, and any reports of pregnancy
- Call patients who discontinue LETAIRIS treatment, or their prescriber, to determine the reason for treatment discontinuation
- Reconcile product distribution data received weekly from the Specialty Pharmacy against the list of enrolled patients in the validated RiskMAP database
- Reconcile reports of pregnancies with the DSPH safety database on a regular basis
- Assist in the conduct of prescriber and patient surveys to evaluate prescriber and patient knowledge, attitudes and behaviors regarding LETAIRIS treatment and the RiskMAP program

#### **6.2.4 Objectives for Specialty Pharmacy**

LETAIRIS will be available only through select Specialty Pharmacies; therefore, distribution will be closely monitored by Gilead. Specialty Pharmacies will be directed to only ship drug to patients who are enrolled in the RiskMAP program. This agreement will be documented in the contract between the Specialty Pharmacies and Gilead.

Specifically, the Specialty Pharmacies must:

- Only ship drug to patients enrolled in the RiskMAP program and only after the authorization to ship drug has been received from the RiskMAP Coordinating Center
- Counsel patients on the risks of LETAIRIS, including the risks of liver injury and serious birth defects
- Counsel patients on the need to complete a monthly liver function test and pregnancy test (for female patients of child bearing potential)
- Counsel all female patients of childbearing potential on the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month after treatment discontinuation (note that if the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, no additional contraception is needed), and the need to inform their prescriber if they suspect they may be pregnant
- Notify Gilead DSPH of any reports of adverse events, including liver injury, and any reports of pregnancy
- Confirm the drug shipment address with the patient
- Call patients, who discontinue LETAIRIS treatment, or their prescriber, to determine the reason for treatment discontinuation
- Provide weekly product distribution data to the RiskMAP Coordinating Center

The controlled distribution system will allow Gilead to track LETAIRIS shipments and review the location and amount of medication shipped to enrolled prescribers and patients.

The Specialty Pharmacies will be audited at the initiation of the RiskMAP program to ensure procedures are in place to support the RiskMAP requirements. Thereafter, Specialty Pharmacies will be included in the company’s annual audit planning.

If Gilead determines that the Specialty Pharmacy is not complying with the RiskMAP program, i.e., is shipping LETAIRIS to patients who are not enrolled in the RiskMAP program, the Specialty Pharmacy may forfeit its authorization to dispense LETAIRIS.

### 6.3 RiskMAP Strategies and Tools

The tools to be used for the LETAIRIS RiskMAP are shown in Table 6. Qualitative testing, including patient comprehension testing and validation, was performed on patient program materials to ensure the key risk messages were clear and could be followed. The prescriber and patient educational brochures, including the PI and Medication Guide, and the results of the qualitative testing are included as Appendices 1 through 4.

**Table 6 RiskMAP Tools by Stakeholder**

Stakeholder	Tool	Description
Prescriber	Prescribing Information	Will include information on: <ul style="list-style-type: none"> <li>• Risk of teratogenicity including:                             <ul style="list-style-type: none"> <li>– Pregnancy category “X”; contraindication</li> <li>– Required pregnancy testing prior to and monthly during LETAIRIS treatment</li> </ul> </li> <li>• Requirement for female patients of childbearing potential to use two different forms of contraception simultaneously</li> <li>• Warning regarding risk of hepatotoxicity and information on required liver function testing prior to and monthly during LETAIRIS treatment</li> <li>• Warning regarding risk of decreased hemoglobin concentration and hematocrit</li> <li>• Discussion of potential risk of reduced male fertility</li> </ul>
	Prescriber Educational Brochure(s)	Describes the risks of LETAIRIS™ and the RiskMAP goals and requirements, including: <ul style="list-style-type: none"> <li>• Prescriber and patient enrollment</li> <li>• Prescriber and patient education</li> <li>• Pregnancy testing requirements</li> </ul>
	Enrollment and Self-attestation Form	Enrolls prescriber into RiskMAP program. Includes self-attestation checklist of all prescriber obligations including: <ul style="list-style-type: none"> <li>• Patient education and counseling</li> <li>• Patient enrollment</li> <li>• Pregnancy and liver function testing requirements</li> </ul>

Stakeholder	Tool	Description
Prescriber, cont.	Sales Force Training Materials	Presentation used by Sales Force to educate prescribers on the RiskMAP program
	Medical Science Liaison (MSL) Training Materials	Presentation used by MSLs to educate prescribers on the RiskMAP program
	Link to RiskMAP program details on Gilead website (www.gilead.com) and product website (www.letairis.com)	Provides program information, including risks of LETAIRIS and RiskMAP program requirements, and all prescriber and patient educational materials and enrollment forms
	RiskMAP Coordinating Center Toll-free help line	Provides health care professionals with medical information concerning LETAIRIS and the RiskMAP program
Patient	Medication Guide	Summarizes important information in language that is easy to read and understand following the FDA specified format.  A Medication Guide will be provided with every prescription of LETAIRIS
	Enrollment and Agreement Form	Includes consent to provide health information and acknowledgement by patients that they will be contacted monthly as part of the RiskMAP program and attestation that they reviewed the Medication Guide and patient educational brochure(s)  Requires prescriber signature acknowledging he/she educated the patient on the risks of LETAIRIS and the requirements of the RiskMAP program and reviewed with the patient the Medication Guide and educational brochure(s).
	Patient Educational Brochure(s)	Describes the risks of treatment with LETAIRIS and the requirements of the RiskMAP program, including the need for liver function testing and pregnancy testing prior to and monthly during LETAIRIS treatment.
	Link to RiskMAP details on Gilead website (www.gilead.com) and product website (www.letairis.com)	Provides program information, including risks of LETAIRIS and requirements of the RiskMAP program and all prescriber and patient educational materials and enrollment forms
	RiskMAP Coordinating Center Toll-free help line	Provides patients with medical information concerning LETAIRIS and the RiskMAP program
RiskMAP Coordinating Center	Contract	The RiskMAP Coordinating Center will have a contract with Gilead that clearly delineates the service provider's responsibilities.
Specialty Pharmacy	Contract	Each Specialty Pharmacy will have a contract with Gilead in which they agree to dispense LETAIRIS only to prescribers and patients who are enrolled in the RiskMAP program
	Inventory Tracking Log	Documentation of dispensing to prescribers and patients enrolled in the RiskMAP program

### **6.3.1 Strategies and Tools for Prescribers**

Prescribers will be informed of the RiskMAP program through instructional materials including the PI, prescriber educational brochure(s), patient educational brochure(s), visits from Gilead's sales force and/or Medical Science Liaisons (MSL), educational programs at professional meetings, and information on the Gilead website (www.gilead.com) and the product website (www.letairis.com).

LETAIRIS prescribers who have been educated about the risks associated with LETAIRIS must enroll in the RiskMAP program in order to prescribe LETAIRIS. Enrollment includes a one-time attestation that the prescriber understands the risks of LETAIRIS and will counsel all patients about these risks of LETAIRIS, will review with each patient the Medication Guide and patient educational brochure(s) and will order and review liver function tests and pregnancy tests (for female patients of childbearing potential) prior to initiation of LETAIRIS treatment and monthly during LETAIRIS treatment.

The prescriber also agrees to educate female patients of child bearing potential on the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation, unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, in which case no additional contraception is needed.

The prescriber educational brochure and enrollment form (Attachment 2) provide the RiskMAP program definition for female patients of childbearing potential as well as information on primary and secondary forms of contraception.

Enrollment forms will be provided by the Gilead sales force and MSLs, or by download from the Gilead website. Prescribers can also call the RiskMAP Coordinating Center using a toll-free telephone number to request an enrollment form or receive information about LETAIRIS and the RiskMAP program.

Prescribers will be required to re-enroll patients into the RiskMAP program after the first 6 months of treatment then annually thereafter. If the patient changes physicians, a new enrollment form will be required. The patient information from the new prescriber will be linked in the RiskMAP program database with information from the prior prescriber. This re-enrollment will serve to reinforce the risks and benefits of LETAIRIS. Prescribers will also be informed of the need to report any adverse events, including liver injury, and any pregnancy that occurs to Gilead.

### **6.3.2 Strategies and Tools for Patients**

To receive LETAIRIS treatment, patients must be enrolled in the RiskMAP program. To enroll a patient in the RiskMAP program, the prescriber will complete a patient enrollment form (Appendix 3) that collects basic patient identifying and contact information as well as insurance coverage data needed to obtain reimbursement for LETAIRIS. The prescriber will also assess whether the patient is a female patient of child bearing potential and, if the patient is of child bearing potential, confirm that a pregnancy test was completed and that the test was negative.

The patient will sign the enrollment form indicating they have read the Medication Guide and patient educational brochure(s) and agree to be contacted for counseling on the RiskMAP program requirements and risks of LETAIRIS and to obtain confirmation that liver function

testing and pregnancy testing (for female patients of childbearing potential) was completed. Female patients of childbearing potential also agree that, if they become pregnant, they will be contacted by the Gilead DSPH Department. The prescriber will also sign the form indicating they have educated the patient on the requirements of the RiskMAP program and the risks of treatment with LETAIRIS and have reviewed the Medication Guide and patient educational brochure(s) with the patient. The form will then be faxed to the RiskMAP Coordinating Center.

Upon receiving the enrollment form, The RiskMAP Coordinating Center will verify that the prescriber indicated (by checking or ticking the appropriate boxes on the patient enrollment form) that the required testing was completed and enter the patient into the database. The RiskMAP Coordinating Center will then authorize the Specialty Pharmacy to ship LETAIRIS. The Specialty Pharmacy will ship LETAIRIS to the patient, as directed.

Patient educational brochures that discuss the appropriate use of LETAIRIS, the risks associated with LETAIRIS treatment and the requirements for receiving LETAIRIS treatment will be sent with the first shipment of LETAIRIS. A Medication Guide will be provided with each 30-day supply of LETAIRIS.

Patients will be called every month by the RiskMAP Coordinating Center to obtain confirmation that liver function testing and pregnancy testing (for female patients of child bearing potential) was completed. If the patient responds affirmatively that he/she has completed the required test(s), the RiskMAP Coordinating Center will provide authorization for the Specialty Pharmacy to dispense a 30-day supply of LETAIRIS.

If the patient is unable to respond affirmatively to completing the required testing, or if the RiskMAP Coordinating Center is unable to reach the patient, the RiskMAP Coordinating Center will contact the patient's prescriber.

All patients will be called by the Specialty Pharmacy, prior to dispensing each 30-day supply of LETAIRIS, to receive counseling on the risks and requirements of LETAIRIS treatment including, the need to have a monthly test to check their liver function and, for female patients of childbearing potential, the need to complete a monthly pregnancy test, to use two different forms of contraception, and to inform their prescriber immediately if they suspect they may be pregnant.

Finally, all patients who discontinue treatment will be called to determine the reason for treatment discontinuation.

### **6.3.3 Strategies and Tools for the RiskMAP Coordinating Center**

Gilead will contract a qualified service provider to serve as the RiskMAP Coordinating Center. By contract, the RiskMAP Coordinating Center will agree to:

- Train all RiskMAP staff on the RiskMAP program procedures and all RiskMAP materials prior to initiation of the RiskMAP Program
- Provide a toll free number that will be appropriately staffed by technical and healthcare professionals to receive calls from prescribers and patients
- Receive and database the prescriber and patient enrollment forms

- Call patients every month to obtain confirmation that liver function testing and pregnancy testing (for female patients of childbearing potential) were completed
- Notify Gilead DSPH of any reports of adverse events, including liver injury, or any report of pregnancy
- Call patients, who discontinue LETAIRIS treatment, or their prescriber, to determine the reason for treatment discontinuation
- Reconcile product distribution data received weekly from the Specialty Pharmacy against the list of enrolled patients in the validated RiskMAP database
- Reconcile reports of pregnancies with the DSPH safety database on a regular basis
- Allow audits by the FDA, Gilead, or a third party designated by Gilead

#### **6.3.4 Strategies and Tools for Specialty Pharmacy**

Gilead will contract select Specialty Pharmacies to distribute LETAIRIS directly to enrolled patients or prescribers. One element of the contract is an agreement to ship LETAIRIS only to enrolled patients.

Specialty Pharmacies will receive authorization to dispense LETAIRIS from the RiskMAP Coordinating Center. LETAIRIS will be packaged in a 30-day supply and will require monthly refills.

Specifically, the designated representative of each Specialty Pharmacy agrees that:

- Training of pharmacy staff on the RiskMAP program procedures and materials has been completed prior to dispensing drug
- LETAIRIS will only be shipped to patients enrolled in the RiskMAP program and only after authorization has been received from the RiskMAP Coordinating Center
- All patients will be counseled on the risks of LETAIRIS treatment, including the risks of liver injury and serious birth defects
- All patients will be counseled on the need to complete monthly liver function testing and pregnancy testing (for female patients of childbearing potential)
- All female patients of childbearing potential will be counseled on the need to use two different forms of contraception, including at least one primary form of contraception, simultaneously during and for one month after treatment discontinuation (unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, in which case no additional contraception is needed) and the need to inform their prescriber if they suspect they may be pregnant
- Gilead will be notified of any reports of adverse events, including liver injury, or any report of pregnancy
- Patients who discontinue LETAIRIS treatment, or their prescriber, will be called to determine the reason for treatment discontinuation
- Each patient will receive a Medication Guide with each LETAIRIS shipment
- An inventory tracking log must be completed for every shipment of LETAIRIS

- The Specialty Pharmacy may be audited by the FDA, Gilead, or a third party designated by Gilead
- Noncompliance with the RiskMAP program could result in loss of the ability to dispense LETAIRIS

#### **6.4 Key Risk Messages**

The key risk messages of the LETAIRIS RiskMAP will be:

- LETAIRIS may cause liver injury
  - LETAIRIS treatment is not recommended for patients with moderate to severe hepatic impairment
  - All patients must have liver function tests (including aminotransferases and bilirubin) before starting LETAIRIS treatment
  - All patients must have liver function tests (including aminotransferases and bilirubin) each month during LETAIRIS treatment
- LETAIRIS can cause major birth defects if taken during pregnancy
  - A woman must not be pregnant when she starts LETAIRIS
  - A pregnancy test must be done before starting LETAIRIS treatment
  - A woman must not become pregnant while being treated with LETAIRIS
  - Pregnancy tests must be done monthly during LETAIRIS treatment
  - Women of childbearing potential must use two different forms of contraception, including at least one primary form of contraception, simultaneously during LETAIRIS treatment and for one month following treatment discontinuation, unless the patient has had a tubal sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, in which case no additional contraception is needed
  - Prescribers should counsel female patients of childbearing potential on suitable forms of contraception or refer the patient to a healthcare professional with expertise in contraception for such counseling

While the key goal of the RiskMAP is to minimize the risks of liver injury and serious birth defects, other risks, including the risk of decreases in hemoglobin concentration and hematocrit and the potential risk of reduced male fertility, will also be addressed in educational materials and tools for prescribers and patients.

#### **6.5 Compliance**

##### **6.5.1 Prescriber Compliance**

Prescriptions written by prescribers who are not enrolled in the RiskMAP program will not be filled by the Specialty Pharmacy. The Specialty Pharmacy will notify the RiskMAP Coordinating Center if a prescription is presented from a prescriber who is not enrolled in the RiskMAP program. The RiskMAP Coordinating Center will call the physician and discuss the requirements of the RiskMAP program and provide him/her with the ability to receive educational materials and an enrollment form.

### 6.5.2 Patient Compliance

Every month the RiskMAP Coordinating Center will call patients to obtain confirmation that liver function testing and pregnancy testing (for female patients of childbearing potential) were completed. If the patient is unable to respond affirmatively that they have completed the required testing, or if the RiskMAP Coordinating Center is unable to reach the patient, the RiskMAP Coordinating Center will contact the patient's prescriber. The RiskMAP Coordinating Center will remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for female patients of childbearing potential).

Patient compliance with liver function and pregnancy testing requirements will be collected and reported on a regular basis.

Any patient who becomes pregnant while treated with LETAIRIS will be followed by the Gilead DSPH Department according to its established internal processes for the term of their pregnancy to assess the outcome of exposure to LETAIRIS. All data collected will be entered into the Gilead DSPH Database (ARISg). Data collected in the database will be used to evaluate the effectiveness of the LETAIRIS RiskMAP by identifying the possible reasons why a patient became pregnant despite the warnings and requirement to complete monthly pregnancy testing prior to receiving LETAIRIS. All pregnancies will be evaluated retrospectively and in aggregate on a regular basis.

Gilead will forward data about all cases of pregnancy received by the DSPH Department to the RiskMAP Coordinating Center for entry into the RiskMAP database. Both databases will be reconciled on a regular basis.

All reports of pregnancy will be reported to the Agency on an expedited basis.

Gilead will also report cases of liver injury to the Agency on an expedited basis. Cases of liver injury that would require expedited reporting will include:

- Cases of liver injury that result in death, hospitalization, liver transplantation or being listed for liver transplantation
- Liver function tests (LFTs) indicating:
  - Serum aminotransferase elevations  $>8x$  the upper limit of normal (ULN); or
  - Serum aminotransferase elevations  $>2xULN$  accompanied by increases in bilirubin  $\geq 2xULN$

### 6.5.3 RiskMAP Coordinating Center Compliance

The RiskMAP Coordinating Center will be audited at the initiation of the RiskMAP Program to ensure procedures are in place to support the RiskMAP requirements. Thereafter the RiskMAP will be included in the company's annual audit planning.

Audits will include, but are not limited to, the following: 1) review of contract in place between Gilead and the RiskMAP Coordinating Center and compliance with requirements of the contract, 2) review RiskMAP Coordinating Center practice for confirming and linking prescriber and patient enrollment in RiskMAP program, 3) confirming that the RiskMAP Coordinating Center is calling patients to obtain confirmation that the required testing was completed, 4) review of process for providing shipment authorization number to the

Specialty Pharmacy, 5) review process for reconciling product distribution data against list of enrolled patients, and 6) review of compliance with other relevant requirements such as adverse event and product complaint reporting procedures.

#### **6.5.4 Specialty Pharmacy Compliance**

If Gilead determines that the Specialty Pharmacy is not complying with the RiskMAP program, i.e., is shipping LETAIRIS to patients who are not enrolled in the RiskMAP program, the Specialty Pharmacy may forfeit its authorization to dispense LETAIRIS.

The Specialty Pharmacies will be audited at the initiation of the RiskMAP Program to ensure procedures are in place to support the RiskMAP requirements.

Thereafter, Specialty Pharmacies will be included in the company's annual audit planning.

Audits will include, but are not limited to, the following: 1) review of contract in place between Gilead and Specialty Pharmacy and compliance with requirements of the contract, 2) review Specialty Pharmacy practice for confirming patient enrollment in RiskMAP program, 3) review of pharmacy dispensing documentation, 4) confirmation of receipt of authorization number by Specialty Pharmacy from RiskMAP Coordinating Center prior to dispensing, 5) confirmation of Specialty Pharmacy counseling patients regarding the risks of LETAIRIS and the requirements of the RiskMAP program, 6) confirmation of any enrollment forms or prescriptions received by the Specialty Pharmacy being routed to the RiskMAP Coordinating Center, and 7) review of compliance with other relevant requirements such as adverse event and product complaint reporting procedures.

### **6.6 LETAIRIS RiskMAP Evaluation**

#### **6.6.1 Core Safety Review Committee**

Gilead is committed to evaluating the effectiveness of the RiskMAP program and reporting results to the FDA quarterly for 2 years after program initiation, then on an annual basis thereafter. Each submission will include data from the RiskMAP program including cases of liver injury and reports of pregnancy exposures.

Specifically, the reports will include:

- Reports of operational audits, including results of distribution data reconciliation
- Results of physician and patient surveys
- The total number of patients and female patients of childbearing potential receiving the product
- Drug use patterns (reasons for use, patient demographics, prescribing medical specialties)
- In the case of pregnancy, the root-cause analysis to determine the reason for the pregnancy exposure
- The number of pregnancy exposures (pregnancy exposures will be recorded within the RiskMAP database as well as the global safety database, with appropriate linkage to allow matching of the cases reported in the RiskMAP database to cases in the global safety database)
- The number (percent) patient reported compliance with:

- Monthly pregnancy testing for female patients of child bearing potential by quarter and overall
- Contraception requirements by quarter and overall
- Liver function testing by quarter and overall
- An analysis of the numbers and reasons for pharmacist calls to prescribers
- The frequency of interruptions in therapy, why such interruptions occurred, and how long the shipment was delayed (e.g., the number of times a shipment was held because the patient had not had their monthly laboratory tests)
- The number and reasons for discontinuation therapy with ambrisentan
- The frequency and reasons for dispensing >30 day supply.

The multidisciplinary Core Safety Review Committee including senior representatives from the Gilead DSPH, Regulatory, Legal, and Clinical departments will review the compiled data and evaluate the effectiveness of the RiskMAP. The Committee will identify areas for improvement, if required.

#### **6.6.2 Compliance Review Subcommittee**

A cross-functional team will be formed that will serve as a Compliance Review Subcommittee. The function of this committee is to facilitate RiskMAP compliance. The committee will meet on a regular basis, and ad hoc as needed, to review results from the monitoring of operational processes, distribution data, and audit data. The committee will determine appropriate corrective action to address non-compliance by stakeholders and ensure continuous improvement of all RiskMAP activities.

#### **6.6.3 Evaluation Measures**

The evaluation measures that will be implemented include surveys of prescribers and patients, auditing of the RiskMAP program processes, and tracking LETAIRIS distribution from the Specialty Pharmacies.

A complete evaluation plan for assessing patient and prescriber knowledge, attitude and behavior and the survey instruments used to collect the information will be submitted to the Agency separately. The anticipated process for administering the surveys follows.

##### **6.6.3.1 Knowledge, Attitude and Behavior Survey of Prescribing Physicians**

On a quarterly basis, the RiskMAP Coordinating Center will administer surveys to a random sample of prescribing physicians. The process for administering surveys will be:

- A random sample to enrolled prescribers will be selected (without replacement)
- The first contact will be by US mail. The mailing will contain the survey and a return postage paid envelope for sending the survey to the RiskMAP Coordinating Center. If the prescribing physician has provided an e-mail address, the survey will also be provided by e-mail. The mailing will include a web address where the prescribing physician can complete the survey online.

- If the physician does not provide a response to the survey within 2 weeks, a fax will be sent to the physician containing the same survey
- If no response is obtained from the fax after a 1-week period, then the physician will be contacted by telephone
- Interviewers at the RiskMAP Coordinating Center will make 3 attempts to reach the physician and administer the survey
- All attempts to contact the physician will be documented

The survey will include questions concerning:

- Prescribing physician knowledge about the benefits and risks of LETAIRIS treatment, including hepatotoxicity and teratogenicity
- Prescribing physician behavior regarding patient counseling, laboratory testing, and pregnancy counseling
- Availability and use of the RiskMAP program patient educational tools in the physician office

#### **6.6.3.2 Knowledge, Attitude and Behavior Survey of Patients**

On a quarterly basis, the RiskMAP Coordinating Center will administer surveys to a random sample of patients who are being treated with LETAIRIS. The process for administering the surveys will be:

- A random sample of enrolled patients will be selected (without replacement). The sample will be stratified by duration of LETAIRIS use, to include new patients (having their first prescription) and patients who have been treated for at least 3 months
- The first contact will be by US mail. The mailing will contain the survey and a return postage paid envelope for sending the survey to the RiskMAP Coordinating Center. If the patient has provided an e-mail address, the survey will also be provided by e-mail. The mailing will include a web address where the prescribing physician can complete the survey online.
- If the patient does not provide a response to the mail survey within 2 weeks, a second mailing will be sent containing the same survey
- If no response is obtained from the second mailing after a 1-week period, then the patient will be contacted by telephone
- Interviewers at the RiskMAP Coordinating Center will make 3 attempts to reach the patient and administer the survey
- All attempts to contact the patient will be documented

The survey will include questions concerning:

- Patient knowledge about the risks of LETAIRIS treatment, including liver injury and serious birth defects
- Patient behavior regarding pregnancy testing and other required testing

- Patient attitude toward contraception (female patients of childbearing potential only)
- Availability and use of the RiskMAP patient educational tools in the physician office

#### **6.6.4 Recommendation Generation and Implementation**

In addition to the individual case evaluation, on an annual basis the Gilead DSPH team will review all information collected during that time period to identify systematic causes for which program changes can be initiated in an effort to reduce the number of pregnancies among women treated with LETAIRIS.

#### **6.6.5 RiskMAP Coordinating Center and Specialty Pharmacy Reconciliation of Inventory and Distribution**

The RiskMAP Coordinating Center will receive product distribution data electronically from each Specialty Pharmacy every week. The RiskMAP Coordinating Center will be responsible for reconciling the product distribution data against the list of enrolled patients in the validated RiskMAP database.

These weekly reconciliations will verify that LETAIRIS is shipped only to patients enrolled in the RiskMAP program.

**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 different reliable 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, right upper stomach 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?”)
- **Low sperm count.** LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

### The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of legs and ankles (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

## How should I store LETAIRIS?

Store LETAIRIS at less than 86 °F (30 °C), in the package it comes in.

## General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about LETAIRIS, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about LETAIRIS. Your doctor can give you information about LETAIRIS that was written for healthcare professionals. Do not use LETAIRIS

for any condition other than that for which it was prescribed. Do not share LETAIRIS with other people. It may harm them.

**Call 1-866-664-LEAP (5327) or visit [www.letairis.com](http://www.letairis.com) or [www.gilead.com](http://www.gilead.com) for more information.**

### **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.

This medication guide has been approved by the U.S. Food and Drug Administration.

Gilead Sciences, Inc., Foster City, CA 94404

June 2007

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GS22-081-000

## LEAP Prescribing Physician Enrollment and Agreement Form

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

### Prescribing Physician 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 # \_\_\_\_\_

### Prescribing Physician Agreement

By signing below, you signify your understanding of the risks of LETAIRIS™ (ambrisentan) treatment and your obligation as a LETAIRIS prescribing physician 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 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 about the need to use 2 different forms of contraception, including at least 1 primary form of contraception, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, no additional contraception is needed.
  - Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner’s vasectomy. A Copper T 380A IUD or LNG 20 IUD can be used alone (i.e., without a secondary form of contraception, as can tubal sterilization).
  - Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.
- I will counsel patients on suitable forms of contraception or refer the patient to a healthcare professional with experience in contraception for 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.
- I agree to re-enroll appropriate patients after the first 6 months and annually thereafter by completing and submitting a new patient enrollment form.

**Prescribing Physician Signature** \_\_\_\_\_ **Date** \_\_\_\_\_

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

Please visit [www.letairis.com](http://www.letairis.com) or [www.gilead.com](http://www.gilead.com) for more information.

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

\*The prescribing physician 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 nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

A woman who has had a tubal sterilization is considered to be of childbearing potential in LEAP.

### **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  $\geq 54$  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 WARNING**.

#### WARNING: POTENTIAL LIVER INJURY

LETAIRIS (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETAIRIS treatment was associated with aminotransferase elevations >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 (>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 thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNG 20 IUD inserted, in which case no other 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, Prescribing and Distribution Program for LETAIRIS*].

## LETAIRIS EDUCATION AND ACCESS PROGRAM (LEAP)

# 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 WARNING**.

  
**Letairis**<sup>™</sup>  
ambrisentan  
5 mg and 10 mg Tablets

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

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



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**Letairis**<sup>™</sup>  
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 WARNING**.

## LEAP Overview

The Prescriber:

- Completes a one-time 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 appropriate patients after the first 6 months and annually thereafter

LEAP:

- Enters every LETAIRIS prescriber and patient in the LEAP database
- Confirms insurance coverage or investigates alternative sources of reimbursement or assistance
- Sends patient information to the chosen specialty pharmacy
- Contacts patients each month to obtain confirmation that they completed the required testing

The Specialty Pharmacy:

- Files the insurance claim
- Answers questions and provides information about LETAIRIS
- Ships LETAIRIS to the patient

## Prescriber Enrollment

Physicians who wish to prescribe LETAIRIS must enroll in LEAP by completing a one-time Prescriber Enrollment and Agreement Form that states they will comply with the program requirements. The Prescriber Enrollment and Agreement Form is in the pocket of the back cover of this brochure.

The prescribing physician 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 prescribed LETAIRIS in LEAP and re-enroll appropriate patients after the first 6 months and annually thereafter.
- Discuss with female patients of childbearing potential the need to use 2 different forms of contraception, including at least 1 primary form of contraception, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation. If the patient has had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, no additional contraception is needed.
  - Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNG 20 IUD can be used alone (i.e., without a secondary form of contraception, as can tubal sterilization).
  - Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.

- 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.

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

## 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. Counsel females of childbearing potential\* on the need to use 2 different forms of contraception, including at least 1 primary form, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation.
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 appropriate patients after the first 6 months and annually thereafter. You will be reminded when re-enrollment is required.

\*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 nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating.

A woman who has had a tubal sterilization is considered to be of childbearing potential in LEAP.

### 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  $\geq 54$  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 the following pages for risks of hepatotoxicity, teratogenicity, decreases in hemoglobin concentration and hematocrit, potential risk of reduced male fertility, coadministration with cyclosporine A, and adverse reactions.

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

# 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  $\geq 2 \times \text{ULN}$  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. Use caution in patients with mild hepatic impairment.

## 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.
- Discuss with female patients of childbearing potential the need to use 2 different forms of contraception, including at least 1 primary form of contraception, simultaneously during LETAIRIS treatment and for 1 month following treatment discontinuation. If the patient has had a tubal

sterilization or a Copper T 380A IUD or LNg 20 IUD inserted, no additional contraception is needed.

- Primary forms of contraception include tubal sterilization, hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring), IUD, and a partner's vasectomy. A Copper T 380A IUD or LNg 20 IUD can be used alone (i.e., without a secondary form of contraception, as can tubal sterilization).
- Secondary forms of contraception include barrier contraceptives such as latex condoms, diaphragms, and cervical caps.
- 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.

## 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.

Hemoglobin must be measured prior to initiation of LETAIRIS and should be measured at 1 month and periodically thereafter. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, discontinuation of treatment should be considered.

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

## Potential Risk of Reduced Male Fertility

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of ERAs in rodents. Patients should be informed of these findings. The impact on human testicular function and male fertility is not known.

## Coadministration With Cyclosporine A

Use caution when LETAIRIS is coadministered with cyclosporine A because cyclosporine A may cause increased exposure to LETAIRIS.

## 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.

Peripheral edema was similar in younger patients ( $< 65$  years) receiving LETAIRIS (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients ( $\geq 65$  years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%, 1/28).

- Read the LETAIRIS full prescribing information and understand the risks of LETAIRIS
- Complete the one-time LEAP Prescriber Enrollment and Agreement Form
- Use the patient Medication Guide and patient brochure to educate patients about the risks of LETAIRIS treatment
- Enroll all patients prescribed LETAIRIS in LEAP
- 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
- Re-enroll appropriate patients after the first 6 months and annually thereafter

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

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



**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.

To enroll a patient in LEAP, please complete and fax this form to LEAP. **FAX: 1-888-882-4035**  
Patient information will be forwarded to the specialty pharmacy you choose.

Accredo  Aetna  Caremark  CIGNA Tel-Drug  CuraScript  Fairview  Walgreens Specialty Pharmacy (Medmark)  WellPoint PrecisionRx

## Patient Information (PLEASE PRINT)

First Name: \_\_\_\_\_ Middle Initial: \_\_\_\_\_ Last Name: \_\_\_\_\_  
SSN #: \_\_\_\_\_ Birthdate: \_\_\_\_/\_\_\_\_/\_\_\_\_ Gender:  M  F  
Address: \_\_\_\_\_ City: \_\_\_\_\_ State: \_\_\_\_\_ ZIP: \_\_\_\_\_  
Day Phone: (\_\_\_\_) \_\_\_\_\_ Evening Phone: (\_\_\_\_) \_\_\_\_\_

**PLEASE FAX COPIES OF ALL RELATED PRIMARY AND SECONDARY INSURANCE INFORMATION TO THE FAX NUMBER ABOVE.**

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 eligibility for benefits; (2) communicate with those covered by this authorization about my medical care; and (3) provide LETAIRIS™ (ambrisentan) support services, including facilitating the provision of LETAIRIS to me. I agree also that Gilead may contact me for reasons related to providing these services. I understand that once my health information has been disclosed to Gilead, federal privacy laws may no longer restrict its use or disclosure. 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. 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 the LEAP program. 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:** \_\_\_\_\_

## Prescribing Physician Information (PLEASE PRINT) Office Contact: \_\_\_\_\_

First Name: \_\_\_\_\_ Last Name: \_\_\_\_\_ State License #: \_\_\_\_\_  
Address: \_\_\_\_\_ City: \_\_\_\_\_ State: \_\_\_\_\_ ZIP: \_\_\_\_\_  
Phone: (\_\_\_\_) \_\_\_\_\_ Fax #: (\_\_\_\_) \_\_\_\_\_ NPI #: \_\_\_\_\_ DEA #: \_\_\_\_\_

**Prescription: LETAIRIS:**  5 mg (30-day supply)  10 mg (30-day supply) Refills: \_\_\_\_\_

Instructions: \_\_\_\_\_

Ship to: Name: \_\_\_\_\_ Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ ZIP: \_\_\_\_\_ Phone: (\_\_\_\_) \_\_\_\_\_

Female patient of childbearing potential  Negative pre-LETAIRIS pregnancy test  
 Patient NOT of childbearing potential  Pre-LETAIRIS liver function tests completed

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

**Diagnosis:**  Primary Pulmonary Hypertension (ICD 416.0)  Pulmonary Hypertension, Secondary (ICD 416.8)  
**Related to:**  Congenital Heart Defects (ICD 745.\_\_\_\_)  Portal Hypertension (ICD 572.3)  Drugs/Toxins (ICD \_\_\_\_)  
 HIV (ICD 042 \_\_\_\_ )  Scleroderma (ICD 710.1)  Lupus (ICD 710.0)  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.

**Prescribing Physician Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

Please visit [www.letairis.com](http://www.letairis.com) or [www.gilead.com](http://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 WARNING** page 30

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#### 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 (4.1)*].

Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNG 20 IUD inserted, in which case no other 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, Prescribing and Distribution Program for LETAIRIS*].

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

Please visit [www.letairis.com](http://www.letairis.com) or [www.gilead.com](http://www.gilead.com) for more information.

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



## LETAIRIS EDUCATION AND ACCESS PROGRAM (LEAP)

# 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 WARNING**.



# 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
- Caremark
- CIGNA Tel-Drug
- CuraScript
- Fairview
- Walgreens Specialty Pharmacy (Medmark)
- WellPoint PrecisionRx

## 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 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.

**While you are 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 2 different forms of contraception, including at least 1 primary form of contraception, at the same time during LETAIRIS treatment and for 1 month following LETAIRIS discontinuation, unless you have had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUD inserted, in which case no other contraception is needed. Talk with your doctor or gynecologist (a doctor who specializes in female reproduction) about the forms of birth control that are suitable for you.

**You must complete all of the tests your doctor orders.** Page 32

**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 (4.1)*]. Pregnancy must therefore be excluded before the initiation of treatment with LETAIRIS and prevented thereafter by the use of at least two reliable methods of contraception unless the patient has had a tubal sterilization or Copper T 380A IUD or LNG 20 IUD inserted, in which case no other 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, Prescribing and Distribution Program for LETAIRIS*].

Please visit [www.letairis.com](http://www.letairis.com) or [www.gilead.com](http://www.gilead.com) for more information.

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



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# 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 WARNING**.



## 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.**  
**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 different reliable 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, right upper stomach 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?”)
- **Low sperm count.** LETAIRIS can lower sperm count in animals. If this happens in men, they may lose the ability to father children. Talk with your doctor if you have any questions or concerns.

#### The most common side effects of LETAIRIS are:

- Lowering of red blood cell count
- Swelling of legs and ankles (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

## Questions to ask your doctor

### How should I store LETAIRIS?

Store LETAIRIS at less than 86°F (30°C), in the package it comes in.

### General information about LETAIRIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you have any concerns or questions about LETAIRIS, ask your doctor or other healthcare provider. This Medication Guide is only a summary of some important information about LETAIRIS. Your doctor can give you information about LETAIRIS that was written for healthcare professionals. Do not use LETAIRIS for any condition other than that for which it was prescribed. Do not share LETAIRIS with other people. It may harm them.

**Call 1-866-664-LEAP (5327) or visit [www.letairis.com](http://www.letairis.com) or [www.gilead.com](http://www.gilead.com) for more information.**

### 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.

“What can I expect from LETAIRIS treatment?”

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

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“What special instructions are there for taking LETAIRIS?”

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

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Robert Temple  
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