



## Therapeutic Class Review<sup>SM</sup>

### Pulmonary Arterial Hypertension – Ambrisentan (Letairis<sup>®</sup>)

December 2007

**New Product for Review:**  
ambrisentan (Letairis<sup>™</sup>) [Gilead]

**Dossier Provided by Manufacturer: Yes**  
**Dossier Evaluation: 3**

- 1 - Dossier missing significant clinical trial(s).
- 2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
- 3 - Mfg. provided all relevant trials and information.

#### Executive Summary

- Pulmonary arterial hypertension (PAH): <sup>[1, 2, 3]</sup>
  - Is a serious disease characterized by progressive increase in pulmonary vascular resistance.
  - Leads to right-sided ventricular dysfunction, decrease in activity tolerance, and may lead to right-sided heart failure and premature death.
  - Includes idiopathic PAH as well as pulmonary hypertension associated with conditions such as connective tissue disease, congenital malformations, HIV-infection, and anorexigen use.
- Life expectancy in patients with PAH depends on the underlying cause of the condition. <sup>[1]</sup>
  - Prior to the availability of targeted therapies for PAH, the median life expectancy from the time to diagnosis for patients with *idiopathic* PAH was 2.8 years.
  - Recent advances in diagnosis and drug therapy in the last decade have extended the life expectancy of these patients.
    - \* Epoprostenol (Flolan) has shown improved survival benefit in patients with class IV symptoms.
- Benchmarks for disease severity, response to therapy, and progression of disease include: <sup>[3]</sup>
  - 6-minute walk distance (6MWD), and
  - New York Heart Association (NYHA)/World Health Organization (WHO) functional class.
- Improvement in the 6MWD in patients with PAH has been correlated to improved survival. <sup>[4, 5]</sup>
- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin and prostacyclin analogs (epoprostenol, treprostinil, and iloprost), endothelin-receptor antagonists (ETAs) (ambrisentan, bosentan), and type 5 phosphodiesterase inhibitors (sildenafil).
- Ambrisentan (Letairis), an oral endothelin-receptor antagonist, was recently approved by the FDA to improve exercise capacity and delay clinical worsening of PAH. <sup>[6]</sup>

- Characteristics of PAH medications:

Medication	Class	Route	Approved for NYHA/WHO Functional class
ambrisentan (Letairis)	ETA	Oral	II and III
bosentan (Tracleer)	ETA	Oral	III and IV
epoprostenol (Flolan)	prostacyclin (synthetic)	Continuous intravenous infusion	III and IV
iloprost (Ventavis)	prostacyclin analog	Inhaled 6 to 9 times daily	III and IV
sildenafil (Revatio)	Type V PDE inhibitor	Oral	Not specified (trials predominantly II and III)
treprostinil (Remodulin)	prostacyclin analog	Continuous subcutaneous or intravenous infusion	II, III, and IV

PDE = phosphodiesterase

- The latest version of the ACCP guideline recommends the addition of an agent from a different class when there is no improvement or deterioration in PAH symptoms with monotherapy.<sup>[3]</sup>
- Letairis is available via a special access program (Letairis Educational Access Program or LEAP) to minimize fetal exposure and the risk of liver injury. This parallels the Tracleer Access Program (T.A.P.) for bosentan (Tracleer).
- Elevation in liver transaminases is a risk with ETAs:
  - The majority information regarding risk of hepatotoxicity comes from experience with bosentan (Tracleer). Elevation in liver transaminases with bosentan (Tracleer) is dose-dependent, occurs both early and late in treatment, and is usually reversible with treatment interruption or cessation.<sup>[7]</sup>
  - Package labelling for ambrisentan (Letairis) also carries warnings of the potential for elevations in liver enzymes.<sup>[6]</sup>

## Evidence

- In two RCTs, ambrisentan (Letairis):
  - Improved exercise capacity in patients with PAH relative to placebo based on 6MWD.
  - Delayed progression of PAH relative to placebo.
- The placebo-adjusted mean change from baseline in the 6MWD ranged from 31 to 59 meters, which is considered a clinically relevant improvement.
- The vast majority of patients in the trials (93%) had WHO class II or III symptoms.
- There is no evidence that ambrisentan (Letairis) is safer or more effective than other medications used for the treatment of PAH.
- There is no evidence that ambrisentan (Letairis) will improve symptoms in patients with inadequate response to other medications used to treat PAH.
- Safety information for ambrisentan is limited to 12 weeks.
  - Adverse events associated with ambrisentan (Letairis) are similar to those seen with bosentan (Tracleer) and include peripheral edema, nasal congestion, flushing and palpitations.
  - Serious adverse events reported in ambrisentan (Letairis) controlled trials include elevation in liver enzymes, anemia, and peripheral edema.

- Ambrisentan (Letairis) was given to 36 patients who discontinued bosentan (Tracleer) or sitaxsentan (an investigational ETA) because of elevations in liver enzymes; however, the trial was not of sufficient design to determine whether ambrisentan (Letairis) is safer than bosentan (Tracleer) with regard to risk of liver toxicity.

## Decision

Ambrisentan (Letairis) is preferred/formulary because:

- There is possibly useful evidence that it improves exercise capacity and delays clinical worsening in patients with PAH.
- It is an additional option for a population with limited options.
- It appears to have an acceptable safety profile relative to other options.

## Products

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s) <sup>b</sup>	FDA approved indications	Usual Dose/Route	Potential Off-label Uses <sup>c</sup>
ambrisentan (Letairis) <sup>[6]</sup>	6/2007	6/2012 (exclusivity – no patent expiration date listed)	Treatment of pulmonary arterial hypertension (PAH) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening.	5 to 10 mg orally once daily	----
bosentan (Tracleer®) <sup>[7]</sup>	11/2001	11/2015	Treatment of pulmonary arterial hypertension (PAH) in patients with WHO class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.	125 mg orally twice daily	Hypertension, Eisenmenger's syndrome
epoprostenol (Flolan®) <sup>[8]</sup>	09/1995	4/2007 (exclusivity – no patent expiration date listed)	1) Long-term intravenous treatment of primary PAH, and 2) Pulmonary hypertension associated with scleroderma spectrum of disease in NYHA Class III and IV patients who do not respond adequately to conventional therapy.	<i>initial/titration:</i> 2 ng/kg/min via intravenous infusion, then increase every 15 minutes by 2 ng/kg/min until adverse effects  (dose highly variable; typically in 20 to 40 ng/kg/min range)	Lung and kidney trans-plantation; cardiopulmonary bypass, myocardial infarction, occlusive stroke, peripheral vascular disease, capillary leak syndrome, angina, peripheral gangrene, ITP
iloprost (Ventavis®) <sup>[9]</sup>	12/2004	12/2011 (exclusivity – no patent expiration date listed)	Treatment of PAH in patients with NYHA Class III or IV symptoms.	2.5 to 5 mcg via inhalation 6 to 9 times per day <i>maximum:</i> 5 mcg per dose; 45 mcg per day	Concomitant treatment with other PAH agents; peripheral vascular disease; angina pectoris
sildenafil (Revatio™) <sup>[10]</sup>	06/2005	3/2012	Treatment of PAH to improve exercise ability.	20 mg orally three times daily	Erectile dysfunction, high altitude pulmonary hypertension, Raynaud's phenomenon
treprostinil (Remodulin®)	05/2002	10/2017	For the treatment of PAH in patients with NYHA Class II to	1.25 ng/kg/min via subcutaneous or	Heart failure, severe peripheral

[11, 12]			IV symptoms to diminish symptoms associated with exercise.	intravenous infusion. Increase in increments of 1.25 ng/kg/min per week; <i>maximum:</i> 40 ng/kg/min.	ischemia
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<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

<sup>b</sup> Based on patents listed in Orange Book as of 08/1/07.

<sup>c</sup> As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

WHO PAH classification = World Health Organization functional classification of PAH

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