

# DRUG DETERMINATION POLICY

**Title:** DDP-29 Pulmonary Arterial Hypertension (PAH) Drugs

**Effective Date:** December 14, 2022



Physicians Health Plan  
PHP Insurance Company  
PHP Service Company

## Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

### 1.0 Policy:

This policy describes the determination process for coverage of specific drugs.

This policy does not guarantee or approve benefits. Coverage depends on the specific benefit plan. Drug Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

### 2.0 Background or Purpose:

PAH medications (Endothelial Receptor Antagonist [ERA], Guanylate Cyclase [sGC] Stimulant, Phosphodiesterase Inhibitors [PDE-5i], or Prostanoids) are specialty drugs indicated for Pulmonary Arterial Hypertension and are associated with significant toxicity. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and acceptable adverse effects.

### 3.0 Clinical Determination Guidelines:

Document the following with chart notes

- I. Pulmonary Arterial Hypertension [must meet all listed below]:
  - A. Prescriber: cardiologist or pulmonologist.
  - B. Diagnosis and severity [must meet both listed below]:
    1. Pulmonary arterial hypertension (PAH) WHO Group I: Confirmed by right heart catheterization or echocardiography [must meet both listed below]:
      - a. Mean pulmonary arterial pressure (mPAP) at least 25 mmHg.
      - b. Pulmonary capillary wedge pressure or left arterial pressure or left ventricular end-diastolic pressure 15mmHg or below.
    2. Vasoreactivity test: completed or documented inappropriateness to test [must meet one listed below]:

- a. Positive test (decrease mPAP at least 10mmHg to less than 40mmHg with unchanged or increased cardiac output) and contraindicated, inadequate response or significant side effects to calcium channel blockers with diltiazem or a dihydropyridine.
- b. Negative response test.

II. Pulmonary Arterial Hypertension therapeutic options (see Appendix II).

A. Treatment naive patient with World Health Organization (WHO) functional class (FC) II or III [must meet one listed below]:

1. Letaris (ambrisentan) and Adcirca (tadalafil) are requested as initial combination therapy.
2. Opsumit (macitentan), Letaris (ambrisentan) or Adempas (riociguat) used as monotherapy [must meet both listed below]:
  - a. Combination therapy with Letaris and Adcirca not tolerated.
  - b. Sildenafil or tadalafil contraindicated, inadequate response or significant adverse effects.
3. Requested drug will be used for add-on therapy to existing monotherapy or dual therapy AND [must meet both listed below]:
  - a. Medications are from different therapeutic classes.
  - b. Unresponsive or progression of disease despite established pulmonary arterial hypertension therapies.

B. WHO functional class III with evidence of rapid disease progression or poor prognosis [must meet one listed below]:

1. Continuous Flolan/Veletri intravenous (epoprostenol IV), Orenitram/Tyvaso/Remodulin intravenous (treprostinil IV) or Remodulin subcutaneous (treprostinil SQ).
2. Addition of inhaled or oral prostanoid if can't manage parenteral prostanoid.

C. WHO functional class IV [must meet one listed below]:

1. Continuous Flolan/Veletri intravenous (epoprostenol), Orenitram/Tyvaso/Remodulin IV (treprostinil) or Remodulin SC (treprostinil).
2. Inhaled prostanoid in combination with an oral PDE-5 inhibitor and an oral endothelin receptor antagonist if can't manage parenteral prostanoid.

D. Patients with inadequate response to initial therapy [must meet one listed below]:

1. WHO functional class III or IV with unacceptable clinical status despite established monotherapy: addition of a second class of PAH therapy.
2. WHO functional class II or IV with unacceptable or deteriorating clinical status despite established therapy with two classes of PAH therapy: addition of third class of PAH therapy.

E. WHO functional class III and IV with inadequate response to maximal pharmacotherapy [must meet one listed below]:

1. Lung transplant candidate.
2. Incorporate palliative care.

III. Approval.

A. Initial: three months.

B. Re-approval: one year (decreased or stabilized pulmonary arterial hypertension WHO functional class and/or decreased or stabilized MPAP).

#### 4.0 Coding:

AFFECTED CODES				
Code	Brand Name	Generic Name	Billing Units (1U)	Prior Approval
J1325	Flolan/Veletri	epoprostenol	0.5mg	Y
J3285	Remodulin	treprostinil	1mg	Y
J7686	Tyvaso	treprostinil	1.74mg	Y
Q4074	Ventavis	iloprost	20mcg	Y

#### 5.0 References, Citations & Resources:

1. Executive summary from the World Symposium on Primary Pulmonary Hypertension 1998, cosponsored by the World Health Organization. Diagnosis and treatment of pulmonary hypertension. American Family Physician. May 1, 2001.
2. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. American College of Cardiology 2009; 53:573-1619.
3. Updated Treatment Algorithm of Pulmonary Arterial Hypertension J Amer Coll of Cardiology 2013; 62 (25):supp D60-72.
4. Lexi comp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Letaris, Tracleer, Opsumit, accessed October. 2021.
5. Lexi comp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Adempas, accessed October 2021.
6. Lexi comp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Revatio, Adcirca accessed October 2021.
7. Lexi comp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Flolan/Velitri, Ventavis, Remodulin. Tyvaso, Uptravi, Orenitram accessed October 2021.
8. Pharmacological Therapy for Pulmonary Arterial Hypertension in Adults: Chest Guidelines and Expert Panel Report. CHEST 2014; 146:449-475.
9. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guidelines and expert panel report. CHEST 2019;155(3):565-586.
10. UpToDate: Treatment of Pulmonary arterial hypertension in adults: Pulmonary HTN-specific Therapy [https://www.uptodate.com/contents/treatment-of-pulmonary-arterial-hypertension-group-1-in-adults-pulmonary-hypertension-specific-therapy?search=treatment%20algorithm%20for%20pulmonary%20arterial%20hypertension%20and%20chronic%20thromboembolic%20pulmonary%20hypertension&source=search\\_result&selectedTitle=7~150&usage\\_type=default&display\\_rank=7](https://www.uptodate.com/contents/treatment-of-pulmonary-arterial-hypertension-group-1-in-adults-pulmonary-hypertension-specific-therapy?search=treatment%20algorithm%20for%20pulmonary%20arterial%20hypertension%20and%20chronic%20thromboembolic%20pulmonary%20hypertension&source=search_result&selectedTitle=7~150&usage_type=default&display_rank=7) accessed October 2021.
12. Guidelines for the treatment of pulmonary arterial hypertension. Lung 2020198:581-596

**6.0 Appendices:**

See pages 5-9.

**7.0 Revision History:**

Original Effective Date: 06/24/2010

Next Review Date:

<b>Revision Date</b>	<b>Reason for Revision</b>
7/19	Moved to new format; replaced abbreviations and modified code table, complete revision of policy to follow 2019 CHEST guidelines
10/20	Annual review; formatting, replaced abbreviations, removed monitoring parameters for mono therapy, approved by P&T Committee 12/9/20
10/21	Annual review; reformatted, added appendix on treatment of pulm. HTN algorithm
10/22	Annual review, Added reference

Appendix I: World Health Organization (WHO) Functional Classifications of Pulmonary Hypertension

<b>Class</b>	<b>Physical Limits</b>	<b>Symptoms (dyspnea, fatigue, chest pain, syncope)</b>
I	No limitation	None upon ordinary physical activity
II	Slight limitation	Symptoms appear upon ordinary physical activity
III	Marked limitation	Symptoms appear upon less than ordinary activity
IV	Inability to carry on any physical activity	Symptoms appear upon any physical activity or may even be present at rest; signs of right heart failure present

## Treatment of pulmonary arterial hypertension algorithm



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If no improvement or patients progress, therapy should be escalated according to WHO functional symptoms. For patients on medications for other conditions, specific drug interactions and management suggestions may be determined by using Lexi-Interact, the drug interactions program included with UpToDate.

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WHO: World Health Organization; IV: intravenous; SC: subcutaneous; INH: inhaled.

\* Acute vasoreactivity testing is typically indicated in patients with WHO class I, II, and III symptoms who have idiopathic, hereditary, or drug/toxin-induced PAH. Contraindications include patients with WHO class IV symptoms, low systemic blood pressure, and low cardiac index.

¶ Endothelin receptor antagonist-phosphodiesterase-5 inhibitor combination is preferred by most experts. Combining phosphodiesterase-5 inhibitors and guanylate cyclase stimulants (riociguat) should be avoided due to the high risk of hypotension.

Δ Options for agents include ambrisentan, bosentan, macitentan, sildenafil, tadalafil, or riociguat. Riociguat is best studied in patients with chronic thromboembolic pulmonary hypertension.

◇ These agents are not approved for this use by regulatory agencies.

§ Some experts use initial combination therapy with a prostanoid and a phosphodiesterase-5 inhibitor.

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*Original figure modified for this publication. Reproduced from: Barst RJ, Gibbs US, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2009; 54:578. Illustration used with the permission of Elsevier Inc. All rights reserved.*

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Appendix III: Agents used for Pulmonary Hypertension

Class	Agent	Class	Dosage
Endothelial Receptor Antagonist (ERA)	Letaris (ambrisentan po)	WHO II, III	<u>Initial:</u> 5mg 1x/day <u>Maximum:</u> 10mg 1x/day
	Opsumit (macitentan po)	WHO II, III	10mg 1x/day
	Tracleer (bosentan)	NYHA II, III, IV	<u>Initial:</u> 62.5mg 2x/day x 4 wks. <u>Maintenance:</u> 125mg 2x/day (>40Kg)
Guanylate Cyclase (sGC) Stimulant	Adempas (riociguat po)	WHO II, III	1mg po 3x/day
Phosphodiesterase Inhibitors (PDE-5i)	Adcirca (tadalafil po)	NYHA II, III	40mg 1x/day
	Revatio (sildenafil po)	NYHA II, III	5mg or 20mg 3x/day
Prostanoids	Uptravi (selexipag po)	WHO II, III	<u>Initial:</u> 200mcg 2x/day <u>Titration:</u> ↑ mcg 2x/day per week (max dose 1,600mcg 2x/day)
	Orenitram (treprostinil po)	WHO II, III	<u>Initial:</u> 0.25mg q 12hrs <u>Titration:</u> ↑ 0.25-0.5mg q 3-4 days
	Tyvaso (treprostinil Inhalation)	NYHA III	<u>Initial:</u> 18mcg (3 inhalations) q 4hrs 4x/day <u>Titration:</u> ↑ 3 inhalations q 1-2wk <u>Maintenance:</u> 54mcg (9 inhalations) 4x/day
	Remodulin (treprostinil SC)	NYHA II, III, IV	<u>Initial:</u> 1.25ng/Kg/min. <u>Titration:</u> ↑ 1.25ng/kg/min/wk x 4 wks ↑ 2.5ng/Kg/min/wk thereafter
	Flolan /Veletri (	NYHA III, IV	<u>Initial:</u> 2ng/Kg/min. infusion <u>Titration:</u> ↑ 1-2ng/Kg/min. q ≥15 mins. <u>Maximum:</u> 195ng/Kg/min.
	Ventavis (iloprost inhalation)	NYHA III, IV	<u>Initial:</u> 2.5mcg/inhalation <u>Maintenance:</u> 2.5-5mcg/inhalation 6-9x/day



Appendix IV: Monitoring & Patient Safety

Drug	Adverse Reactions	Monitoring	REMS
Endothelial Receptor Antagonist (ERA)  Letaris Tracleer Opsumit	<ul style="list-style-type: none"> <li>• Cardiovascular: peripheral edema (11-29%)</li> <li>• Central Nervous System : headache (14-15%)</li> <li>• Hematology: anemia (11-13%),</li> <li>• Respiratory: respiratory. tract infection (20-22%),</li> <li>• Pregnancy Category X</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiovascular: signs and symptoms of peripheral edema</li> <li>• Hepatic: LFTs pre and during; liver injury signs and symptoms</li> <li>• Hematology: Hgb and Hct prior and during therapy</li> <li>• Pregnancy test: pre/post and monthly during</li> </ul>	<ul style="list-style-type: none"> <li>• Purpose: warn re pregnancy precautions</li> <li>• Prescribers and pharmacy enrolled in Opsumit, Tracleer, Letaris REMS, read medication guide and review pregnancy. tests</li> <li>• Med. guide: dispense w product</li> <li>• Web sites:  <a href="http://www.opsumitrems.com/">http://www.opsumitrems.com/</a>,  <a href="http://www.tracleer.com/Hcp-Healthcare-Professionals">http://www.tracleer.com/Hcp-Healthcare-Professionals</a> ,  <a href="http://www.letarisrems.com/REMS_Program.asp">http://www.letarisrems.com/REMS_Program.asp</a>  <a href="https://www.adempasrems.com">x (https://www.adempasrems.com)</a>.                     </li> </ul>
Guanylate Cyclase (sGC) Stimulant  Adempas	<ul style="list-style-type: none"> <li>• Cardiovascular: hypotension (3-10%)</li> <li>• Central Nervous System: headache (27%), dizziness (20%),</li> <li>• Gastrointestinal: dyspepsia (13-19%), N/V (10-14%), diarrhea (12%),</li> <li>• Pregnancy Category X</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiovascular: blood pressure, peripheral edema signs and symptoms</li> <li>• Respiratory. ↑ function, PFT exercise tolerance</li> <li>• Pregnancy test: pre/post and monthly during</li> </ul>	<ul style="list-style-type: none"> <li>• Not needed</li> </ul>
Phosphodiesterase Inhibitors (PDE-5i)  Revatio Adcirca	<ul style="list-style-type: none"> <li>• Cardiovascular: flushing (1-19%)</li> <li>• Central Nervous System: headache (3-46%)</li> <li>• GI: dyspepsia (1-17%), nausea (10-11%)</li> <li>• Neuromuscular/Musculoskeletal: myalgia (1-14%), back/extremity pain (1-12%)</li> <li>• Respiratory: respiratory tract inf. (3-13%), epistaxis (9-13%)</li> <li>• Pregnancy Category B</li> </ul>	<ul style="list-style-type: none"> <li>• Response to therapy</li> <li>• Cardiovascular: blood pressure, heart rate</li> <li>• Respiratory: pulmonary edema signs and symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Not needed</li> </ul>
Prostanoids  Flolan/Veletri Ventavis Remodulin Tyvaso Uptravi Orenitram	<ul style="list-style-type: none"> <li>• Cardiovascular: increased heart rate (35-43%), flushing (23-42%), hypotension (13%)</li> <li>• Central Nervous System: dizziness (83%), headache (46-83%), chills (25%), fever (25%), flu-like Sx (25%), sepsis (25%), anxiety (21%), tremor (21%), agitation (11%)</li> <li>• Dermatology: ulcer (39%), eczema (25%), skin rash (25%), urticarial (25%)</li> <li>• GI: diarrhea (25%), nausea (22-41%)</li> <li>• Local: infusion pain (85%), site reaction (83%)</li> <li>• Miscellaneous: jaw pain (13-54%)</li> <li>• Pregnancy Category B</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiovascular: blood pressure, heart rate</li> <li>• Local: infusion site symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Not needed</li> </ul>