&T DRUG DETERMINATION POLICY

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

Effective Date: 12/15/2020

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

A. Pulmonary Arterial Hypertension [must meet all listed below]:

   1. Prescriber: cardiologist or pulmonologist.

   2. Diagnosis and severity:[must meet both listed below]:

      a. Pulmonary arterial hypertension (PAH) WHO Group I: Confirmed by right heart catheterization or echocardiography [must meet both listed below]:

         - Mean pulmonary arterial pressure (mPAP) at least 25 mmHg.

         - Pulmonary capillary wedge pressure or left arterial pressure or left ventricular end-diastolic pressure 15mmHg or below.

      b. Vasoreactivity test: completed or documented inappropriateness to test [must meet one listed below]:

- Positive test (decrease mPAP at least10mmHg 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.

- Negative response test.

B. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) [must meet both listed below]:

1. Prescriber: cardiologist of pulmonologist.

2. Diagnosis and severity [must meet one listed below]:

a. Persistent or recurrent CTEPH after surgical treatment (pulmonary endarterectomy) or inoperable [must meet all listed below]:

- Mean pulmonary arterial pressure (mPAP) at least 25 mmHg.

- Pulmonary capillary wedge pressure 15mmHg or below.

- Thromboembolic occlusion of the proximal or distal pulmonary vasculature from computed tomographic angiography (CT-PA) or ventilation-perfusion (V/Q) lung scan.

C. Pulmonary Arterial Hypertension (PAH) therapeutic options

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

a. Letaris (ambrisentan) and Adcirca (tadalafil) are requested as initial combination therapy.

b. Opsumit (macitentan), Letaris (ambrisentan) or Adempas (riociguat) used as monotherapy [must meet both listed below]:

- Combination therapy with Letaris and Adcirca not tolerated.

- Sildenafil or tadalafil contraindicated, inadequate response or significant adverse effects.

c. Requested drug will be used for add-on therapy to existing monotherapy or dual therapy AND [must meet both listed below):

- Medications are from different therapeutic classes.

- Unresponsive or progression of disease despite established PAH therapies.

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

a. Continuous Flolan/Veletri intravenous (epoprostenol IV), Orenitram/Tyvaso/Remodulin intravenous (treprostinil IV) or Remodulin subcutaneous (treprostinil SQ).

b. Addition of inhaled or oral prostanoid if can’t manage parenteral prostinoid.

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

a. Continuous Flolan/Veletri intravenous (epoprostenol), Orenitram/Tyvaso/Remodulin IV (treprostinil) or Remodulin SC (treprostinil).

b. Inhaled prostinoid in combination with an oral PDE-5 inhibitor and an oral endothelin receptor antagonist if can't manage parenteral prostinoid.

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

a. WHO functional class III or IV with unacceptable clinical status despite established monotherapy: addition of a second class of PAH therapy.

b. 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.

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

a. Lung transplant candidate.

b. Incorporate palliative care.

D. Persistent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) therapy [must meet one listed below]:

1. Treatment of WHO functional class II to III: Adempas (riociguat).

2. Treatment of WHO functional class II to IV: Tracleer (bosentan).

3. Treatment of severely ill WHO functional class IV [must meet one listed below]:

a. Continuous Flolan/Veletri intravenous (epoprostenol IV), Orenitram/Tyvaso/Remodulin intravenous (treprostinil IV) or Remodulin subcutaneous (treprostinil SQ).

b. Inhaled prostinoid in combination with an oral PDE-5 inhibitor and an oral endothelin receptor antagonist if can't manage parenteral prostinoid.

E. Approval.

1. Initial: three months.

2. 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	ilopprost	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 Cardiaology 2013; 62 (25):supp D60-72.
4. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Letaris, Tracleer, Opsumit, accessed October. 2020.
5. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Adempas, accessed October 2020.
6. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Revatio, Adcirca accessed October 2020.
7. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Flolan/Velitri, Ventavis, Remodulin. Tyvaso, Uptravi, Orenitram accessed October 2020.
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.

6.0 Appendices:

See pages 5-7.

7.0 Revision History:

Original Effective Date: 06/24/2010

Next Review Date: 11/10/2021

Revision Date	Reason for Revision
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

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

Class	Physical Limits	Symptoms (dyspnea, fatigue, chest pain, syncope)
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

Appendix II: Agents used for Pulmonary Hypertension

Class	Agent	Class	Dosage
Endothelial Receptor Antagonist (ERA)	Letaris (ambrisentan po)	WHO II, III	Initial: 5mg 1x/day Maximum: 10mg 1x/day
	Opsumit (macitentan po)	WHO II, III	10mg 1x/day
	Tracleer (bosentan)	NYHA II, III, IV	Initial: 62.5mg 2x/day x 4 wks. Maintenance: 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	Initial: 200mcg 2x/day Titration: ↑ mcg 2x/day per week (max dose 1,600mcg 2x/day)
	Orenitram (treprostinil po)	WHO II, III	Initial: 0.25mg q 12hrs Titration: ↑ 0.25-0.5mg q 3-4 days
	Tyvaso (treprostinil Inhalation)	NYHA III	Initial: 18mcg (3 inhalations) q 4hrs 4x/day Titration: ↑ 3 inhalations q 1-2wk Maintenance:54mcg (9 inhalations) 4x/day
	Remodulin (treprostinil SC)	NYHA II, III, IV	Initial: 1.25ng/Kg/min. Titration: ↑ 1.25ng/kg/min/wk x 4 wks ↑ 2.5ng/Kg/min/wk thereafter
	Flolan /Veletri (	NYHA III, IV	Initial: 2ng/Kg/min. infusion Titration: ↑ 1-2ng/Kg/min. q ≥15 mins. Maximum: 195ng/Kg/min.
	Ventavis (iloprost inhalation)	NYHA III, IV	Initial: 2.5mcg/inhalation Maintenance: 2.5-5mcg/inhalation 6-9x/day

Appendix III: Monitoring & Patient Safety

Drug	Adverse Reactions	Monitoring	REMS
Endothelial Receptor Antagonist (ERA) Letaris Tracleer Opsumit	• Cardiovascular: peripheral edema (11-29%) • Central Nervous System : headache (14-15%) Hematology: anemia (11-13%), • Respiratory: respiratory. tract infection (20-22%), • Pregnancy category X	• Cardiovascular: signs and symptoms of peripheral edema • Hepatic: LFTs pre and during; liver injury signs and symptoms • Hematology: Hgb and Hct prior and during therapy • Pregnancy test: pre/post and monthly during	• Purpose: warn re pregnancy precautions • Prescribers and pharmacy enrolled in Opsumit, Tracleer, Latairis REMS, read medication guide and review pregnancy. tests • Med. guide: dispense w product • Web sites: http://www.opsumitrems.com/, http://www.tracleer.com/Hcp-Healthcare-Professionals , http://www.letairisrems.com/REMS_Program.aspx (https://www.adempasrems.com).
Guanylate Cyclase (sGC) Stimulant Adempas	• Cardiovascular: hypotension (3-10%) • Central nervous system: headache (27%), dizziness (20%), • Gastrointestinal: dyspepsia (13-19%), N/V (10-14%), diarrhea (12%), • Pregnancy category X	• Cardiovascular: blood pressure, peripheral edema signs and symptoms • Respiratory. ↑function, PFT exercise tolerance • Pregnancy test: pre/post and monthly during	
Phosphodies-terase Inhibitors (PDE-5i) Revatio Adcirca	• Cardiovascular: flushing (1-19%) • Central nervous system: headache (3-46%) • GI: dyspepsia (1-17%), nausea (10-11%) • Neuromuscular/musculo-skeletal: myalgia (1-14%), back/extremity pain (1-12%) • Respiratory: respiratory tract inf. (3-13%), epitaxis (9-13%) • Pregnancy category B	• Response to therapy • Cardiovascular: blood pressure, heart rate • Respiratory: pulmonary edema Signs and Symptoms	• Not needed
Prostanoids Flolan/Veletri Ventavis Remodulin Tyvaso Uptravi Orenitram	• Cardiovascular: increased heart rate (35-43%), flushing (23-42%), hypotension (13%) • Central nervous system: dizziness (83%), headache (46-83%), chills (25%), fever (25%), flu-like Sx (25%), sepsis (25%), anxiety (21%), tremor (21%), agitation (11%) • Dermatology: ulcer (39%), eczema (25%), skin rash (25%), urticarial (25%) GI: diarrhea (25%), nausea (22-41%) • Local: infusion pain (85%), site reaction (83%) • Miscellaneous: jaw pain (13-54%) • Pregnancy category B	• Cardiovascular: blood pressure, heart rate • Local: infusion site symptoms	• Not needed