COLLEGE OF PHARMACY
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UTAH MEDICAID DUR REPORT

APPROVED THERAPIES FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION IN ADULTS

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(PLEASE REFER TO FULL REPORT)

Background: Pulmonary Arterial Hypertension (PAH)

- Caused by vasculopathy of the pulmonary artertial vasculature
  - *Extensive remodeling* (eg, thickening, fibrosis)
  - *Endothelial dysfunction*: impaired vasodilator production (nitric oxide and prostacyclin) and overproduction of vasoconstrictors (endothelin-1)
  - *Vessel narrowing*
    - Increased pulmonary arterial pressure and resistance

      Pulmonary hypertension (PH): *mPAP >20 mmHg*

      PAH is characterized by pre-capillary PH: *mPAP >20 mmHg, **plus** PAWP ≤15 mmHg and PVR >2 WU or >3 WU (depending on the guideline)*
    - Right ventricular overload and remodeling
    - Heart failure, reduced quality of life, and premature death

- Signs and symptoms:
  - Dyspnea, reduced physical performance and/or fatigue, weakness, palpitations, lightheadedness.
  - Progressive symptoms include edema, ascites, abdominal distention, hemoptysis, arrhythmias, enlarged jugular veins, tachycardia, and pleural effusion

Background

- PAH is a rare disorder: 5 to 52 cases per million persons based on European registries
- Ideally, patients with PAH should be evaluated and managed by providers in pulmonary hypertension centers of expertise
- Classified as **Group 1** Pulmonary Hypertension (**PH**), out of 5 PH groups
  - Group 1 (PAH) is further sub-classified according to the etiology
    1. **Idiopathic PAH (IPAH)**
    2. **PAH associated with**
       a) **connective tissue disease** (**PAH-CTD**)
       b) **congenital heart disease**
       c) **portal hypertension** (**PAH-PoPH**)
       d) **drugs/toxins** (**DPAH):** eg, dasatinib, sofosbuvir, methamphetamines
       e) HIV infection (PAH-HIV)
       f) schistosomiasis
    3. Heritable PAH (HPAH): with known associated genetic mutations
    4. PAH with venous/capillary involvement: pulmonary venoocclusive disease, and/or pulmonary capillary hemangiomatosis
    5. Persistent PH of the newborn

Disease Severity

- ✓ Multi-parametric assessment is used to determine disease severity and inform therapeutic decisions
  - World Health Organization Functional Class (**WHO-FC**) for Pulmonary Hypertension (**PH**)
  - exercise capacity
  - echocardiographic, laboratory, and hemodynamic variables

WHO-FC classes

- **WHO-FC I**: PH is present but does not limit physical activity. Dyspnea, fatigue, chest pain, or near syncope are not experienced with ordinary activity.
- **WHO-FC II**: PH slightly limits physical activity. The patient is comfortable at rest but ordinary physical activity causes dyspnea, fatigue, chest pain, or near syncope.
- **WHO-FC III**: PH results in marked physical activity limitations. Patients are comfortable at rest, but less than ordinary activity induces dyspnea, fatigue, chest pain, or near syncope.
- **WHO-FC IV**: PH results in symptoms at any physical intensity level. Symptoms (eg, dyspnea and/or fatigue) may be present at rest and there are signs of right-sided heart failure. Discomfort generally increases as the intensity of physical activity increases.

PAH Pharmacotherapy

- Therapies FDA-approved for PAH (ie, WHO Group 1 PH)

Prostacyclin pathway agonist		Endothelin receptor antagonist (ERA)	Nitric oxide-soluble guanylate cyclase- cyclic guanosine monophosphate (NO-sGC-cGMP) pathway enhancer	
epoprostenol (IV) iloprost (INH) treprostinil (IV, SC, INH, PO)	**Prostacyclin Analogs**	ambrisentan (PO) bosentan (PO) macitentan (PO)	sildenafil (PO, IV) tadalafil (PO)	**Phospho-diesterase-5 Inhibitor (PDE5i)**
selexipag (IV, PO)	**Prostacyclin Receptor Agonist**		riociguat (PO)	**Soluble Guanylate Cyclase (sGC) Stimulator**

Abbreviations: INH, inhalation, IV, intravenous, PO, oral, SC, subcutaneous

- For a subset of cases, off-label use of a high-dose calcium channel blocker (CCB) may be an option

PAH-specific Agents: Indications

The reviewed PAH drugs are labeled for the treatment of PAH for a variety of clinical objectives:

a) *To delay disease progression*: oral treprostinil, selexipag

b) *To reduce the risk of disease progression*: macitentan, ambrisentan/tadalafil

c) *To delay clinical worsening*: ambrisentan, sildenafil, riociguat

d) *To decrease clinical worsening*: bosentan in adult patients

e) *To reduce the risk of PAH-related hospitalization*: selexipag, ambrisentan/tadalafil, macitentan

f) *To improve exercise capacity*: epoprostenol, treprostinil, ambrisentan, ambrisentan/tadalafil, bosentan, sildenafil, tadalafil, riociguat

g) *To improve WHO-functional class*: riociguat

h) *To improve endpoint of exercise tolerance, symptoms, and lack of deterioration*: iloprost

i) *To reduce the rate of clinical deterioration when transitioning from epoprostenol*: injectable treprostinil

j) *To improve pulmonary vascular resistance*: bosentan in pediatric patients

<u>Non-PAH Approved Indications</u>

- Tyvaso DPI (treprostinil) approved for PH associated with interstitial lung disease (Group 3 PH)
- Riociguat approved for persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH; WHO Group 4) after surgical treatment or inoperable CTEPH

Clinical Treatment Guidelines

2022 European Society of Cardiology and the European Respiratory Society (**ESC/ERS**) Pulmonary Hypertension Guideline

2019 American College of Chest Physicians (**ACCP**) Pulmonary Arterial Hypertension Guideline

High-dose Calcium Channel Blockers (**CCBs**)

- Candidacy for CCBs is determined by vasoreactivity testing (**VT**) during right heart catheterization
  - VT recommended only for certain subtypes of PAH:
    - **IPAH, HPAH, or DPAH** (2022 ESC/ERS)
    - testing patients outside of these subtypes is specifically recommended *against*
  - Supportive evidence for CCBs in PAH (off-label) is generally graded as low-level evidence
  - CCBs should not be used for (or may not be favorable for)

    a) empiric treatment of PAH (ie, when VT cannot be carried out or is too risky)
      - Increased risk of adverse events during vasoreactivity testing: those with **WHO FC-IV**, low systemic blood pressure, low cardiac output, or pulmonary veno-occlusive disease

    b) for PAH that is non-vasoreactive

    c) in the presence of right ventricular failure

    d) when there are contraindications to CCBs

    e) inadequate evidence supporting the use in a particular PAH subtype (eg, PAH-CTD)

Patients with PAH who are not candidates for vasoreactivity testing or CCB should be initiated on drugs approved for PAH

Treatment Approach with PAH-specific Therapies

Treatment-naive patients (ie, no previous PAH-approved drug therapy)

ACCP 2019

- Initiate when presenting in WHO-FC II or higher if not a candidate for CCB or with insufficient response to CCB
  - Presenting in **FC II or III:** initial combination therapy with ambrisentan and tadalafil, or montherapy with ERA, PDE5i, or riociguat
  - Presenting in **FC III plus** rapid progression of disease or markers for poor prognosis: initial therapy with parenteral prostenoid
  - Presenting in **FC IV**: initial therapy with parenteral prostenoid, or secondarily, inhaled prosteoid with oral PDE5i or ERA

2022 ESC/ERS

- Risk for poor prognosis, based on multi-parameter assessment

Treatment-experienced patients: escalate therapy, adding a second or third agent from a different drug class if unacceptable clinical status remains (ie, insufficient response from initiated mono- or dual-therapy)

Treatment Approach

2022 ESC/ERS

Patients who are not candidates for CCB therapy **or** who had insufficient* response to CCB

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PAH-specific drug regimen is initiated

- Initial drug regimen chosen based on:
  - **Presence of cardiopulmonary co-morbidities****
  - **PAH subtype**
  - **Mortality risk**: 3-risk strata, multi-parametric assessment for mortality at 1 year

*When any of the following are not met: BNP <50 ng/L, NT-proBNP <300 ng/L, and normal or near-normal resting hemodynamic parameters (eg, mPAP<30 mmHg, PVR <4 WU)

** CV comorbidities are risk factors for left ventricular diastolic dysfunction including obesity, diabetes, coronary heart disease, HTN, and/or a low lung diffusion capacity for carbon monoxide

3-Strata Risk Assessment Tool for Initial Therapy Decision-making, 2022 ESC/ERS Guideline			
Determinants of prognosis	**Low risk (<5% estimated 1-year mortality)**	**Intermediate risk (5–20% estimated 1-year mortality)**	**High risk (>20% estimated 1-year mortality)**
Signs of right HF	None	None	Present
Progression of symptoms and clinical manifestations	None	Slow	Rapid
WHO-FC	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Biomarkers BNP or NT- proBNP	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Cardiopulmonary exercise testing	Peak VO_2>15 mL/min/kg (>65% predicted) VE/VCO_2 slope<36	Peak VO_2 11–15 mL/min/kg (35–65% predicted) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% predicted) VE/VCO_2 slope >44
Syncope	None	Occasional with heavy exercise or occasional syncope in a stable patient	Repeated, with little or regular physical activity
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m2 RVESVI >54 mL/m2
Hemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SVI <31 mL/m^2 SvO_2 <60%

Abbreviations: 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO2, ventilatory equivalents for carbon dioxide; VO2, oxygen uptake; WHO-FC, World Health Organization functional class.

2022 ESC/ERS

Treatment-naive patients

- Monotherapy (**PDE5i or ERA**), typically initiated for patients
  - with *cardiopulmonary co-morbidities* (all risk categories)

    and/or
  - with PAH associated with HIV or portal hypertension

- Dual therapy (**PDE5i & ERA**)
  - IPAH, HPAH, DPAH, or PAH-CTD
  - **without** cardiopulmonary comorbidities,

    and
  - low or intermediate risk of death

- Initial triple therapy (**PDE5i, an ERA, & injectable prostacyclin analog**)
  - IPAH, HPAH, DPAH, or PAH-CTD
  - **without** cardiopulmonary comorbidities

    and
  - high risk of death, or intermediate risk of death with severe hemodynamic impairment

2022 ESC/ERS

Treatment-experienced patients (eg, at follow-up)

✓ 4-risk strata multi-parameter tool to guide treatment decisions for escalating therapy

	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
Points assigned for each variable[a]	**1**	**2**	**3**	**4**
WHO-FC	I or II	-	III	IV
6MWD (meters)	>440	320–440	165–319	<165
BNP or NT-proBNP (ng/L)	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100

[a] *Risk is calculated by dividing the sum of points for each variable and by the number of variables and rounding to the next integer*

Low risk: Continue initiated regimen

Intermediate risk:

- Many options for sequential therapy for double- or triple-combination regimens
  - Eg, add selexipag to ERA/PDE5i therapy; switch from PDE5i to riociguat; add inhaled or oral prostacyclin analog

Intermediate-high or high risk:

- Add continuous IV or SC infusion of prostacyclin analog
  - Or if parenteral prostacyclin analog is unfeasible, use selexipag or switch from PDE5i to riociguat
  - Other double- or triple-combination regimens can be considered

Prior Authorization (PA) Criteria for PAH Drug Therapies

Nitric Oxide-cGMP Enhancers

Adcirca (tadalafil), Adempas (riociguat), Alyq (tadalafil), Revatio (sildenafil)

Prostacyclin pathway therapies

Flolan (epoprostenol), Veletri (epoprostenol), Ventavis (iloprost), Orenitram (treprostinil), Remodulin (treprostinil), Tyvaso (treprostinil), Uptravi (selexipag)

Endothelin receptor antagonists

Letairis (ambrisentan), Tracleer (bosentan), Opsumit (macitentan)

Current PA Criteria	Considerations and Possible Modifications
Right heart catheterization & documentation of *mPAP*	May clarify which mPAP measurement is requested and consider cases that cannot undergo right heart catheterization (RHC): • *historical* mPAP (prior to PAH treatment) to support the PAH diagnosis • If the patient is unable to undergo RHC, state reason and, if provider is not with a PH specialty center, attest to consultation with a PH specialty center to support PAH diagnosis.
Requirement for vasoreactivity testing & step through CCB	Not all subtypes of PAH are indicated for vasoreactivity testing (per 2022 European guideline); and not all patients with PAH may be appropriate for off-label use of CCB therapy. • Consider adding a field for the provider to attest that vasoreactivity testing and/or CCB therapy is inappropriate for their patient if unable to meet the current criteria • Alternatively, the criteria may be considered for removal
Requirement for WHO-FC II or worse in order to receive PAH therapy	May consider removal of this criterion in order to ensure that patients are able to • receive continued PAH therapy to maintain an improved clinical status which may include WHO-FC I • switch between therapies for purposes of tailoring therapy to the patient's needs while improved to WHO-FC I Alternatively, rewording may be considered to prevent miss-application to treatment-experienced patients (eg,"Patient has **a history of** WHO-FC II, III, or IV," to not be confused with their current status).

Current PA Criteria	Considerations and Possible Modifications
Re-authorization & requirement for positive clinical response (eg, 6MWT and FEV1)	PAH requires consistent, life-long treatment. Sudden interruption in therapy can led to exacerbation/ hospitalization. • May consider extending re-authorization frequency to every 9 or 12 months to minimize the potential for treatment interruptions • May consider removing the requirement to demonstrate a positive clinical response since it may not be sensitive to nuances of the disease. OR • Consider additional markers for improved disease severity aside from 6MWT (see risk-strata tables), and patient-specific goals expressed by provider • Consider the unique approved indications of PAH agents (eg, indicated to reduce the risk for (or delay) disease progression, etc; see slide 6)

Utilization Medicaid Fee-for-service Claims for **Adults**, 2022

Pharmacy Claims

Over the 1 year period, there were:

- **24 adults who utilized a PAH drug of interest (127 total claims)**
  - generic sildenafil: 37% of total claim counts
  - generic tadalafil: 26%
  - Opsumit (macitentan): 21%
  - ambrisentan (primarily as Letairis): 11%
  - <5% each: Tyvaso [treprostinil] inhalation, and Uptravi [selexipag] tablets
  - no pharmacy claims were found for epoprostenol, iloprost, bosentan, or riociguat

Medical Claims

Over the 1 year period, there were:

- **Less than 5 adults** who received a PAH drug
- The 15 total medical claims consisted of
  - Remodulin injection (treprostinil), Opsumit (macitentan), and sildenafil

Thank you

REFERENCES

Slide 2

- Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *European Heart Journal*. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237 Accessed 11/21/2022. Available at https://doi.org/10.1093/eurheartj/ehac237
- Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43(12, Supplement):S13-S24. doi:https://doi.org/10.1016/j.jacc.2004.02.029 https://www.sciencedirect.com/science/article/pii/S0735109704004383
- Rubin L, Hopkins W. The epidemiology and pathogenesis of pulmonary arterial hypertension (Group 1). UpToDate.com; 2022. Last Updated November 28, 2022. Available at https://www.uptodate.com/contents/the-epidemiology-and-pathogenesis-of-pulmonary-arterial-hypertension-group-1?topicRef=8250&source=see_link#H4023264274
- Pietra GG, Capron F, Stewart S, et al. Pathologic assessment of vasculopathies in pulmonary hypertension. *J Am Coll Cardiol*. 2004;43(12, Supplement):S25-S32. doi:https://doi.org/10.1016/j.jacc.2004.02.033 https://www.sciencedirect.com/science/article/pii/S0735109704004425

Slide 3

- Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *European Heart Journal*. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237 Accessed 11/21/2022. Available at https://doi.org/10.1093/eurheartj/ehac237
- Rubin L, Hopkins W. The epidemiology and pathogenesis of pulmonary arterial hypertension (Group 1). UpToDate.com; 2022. Last Updated November 28, 2022. Available at https://www.uptodate.com/contents/the-epidemiology-and-pathogenesis-of-pulmonary-arterial-hypertension-group-1?topicRef=8250&source=see_link#H4023264274
- Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary Arterial Hypertension: Baseline Characteristics From the REVEAL Registry. *Chest*. 2010;137(2):376-387. doi:https://doi.org/10.1378/chest.09-1140 https://www.sciencedirect.com/science/article/pii/S0012369210600827

Slide 4, 5

- Klinger JR, Elliott CG, Levine DJ, et al. Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report. *Chest*. 2019;155(3):565-586. doi:https://dx.doi.org/10.1016/j.chest.2018.11.030 Accessed 20190117//. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med16&NEWS=N&AN=30660783
- Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *European Heart Journal*. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237 Accessed 11/21/2022. Available at https://doi.org/10.1093/eurheartj/ehac237

Slide 6

- Opsumit (macitentan) tablets, for oral use. Package Insert. Actelion Pharmaceuticals US Inc. a Janssen Pharmaceutical Company; July 2022.
- Letairis (ambrisentan) tablets, for oral use. Package Insert. Gilead Sciences Inc; October 2019.
- Tadliq (tadalafil) oral suspension. Package Insert. CMP Pharma Inc; June 2022.
- Ventavis (iloprost) inhalation solution, for oral inhalation use. Package Insert. Actelion Pharmaceuticals US Inc.; March 2022.
- Tyvaso (treprostinil) inhalation solution, for oral inhalation use. Package Insert. United Therapeutics Corp.; May 2022.
- Uptravi (selexipag) oral tablets and intravenous injection. Package Insert. Actelion Pharmaceuticals US Inc. a Janssen Pharmaceutical Company; July 2022.
- TRACLEER (bosentan) tablets, for oral use and for oral suspension. Package Insert. Actelion Pharmaceuticals US Inc. a Janssen Pharmaceutical Company; July 2022.
- Revatio (sildenafil) oral tablets, oral supension, and injection for intravenous use. Package Insert. Pfizer Labs; July 2020.
- Adempas (riociguat) tablets, for oral use. Package Insert. Bayer HealthCare Pharmaceuticals Inc.; September 2021.
- Tyvaso DPI (treprostinil) inhalation powder, for oral inhalation use. Package Insert. United Therapeutics Corp.; May 2022.
- Veletri (epoprostenol) for injection. Package Insert. Actelion Pharmaceuticals Inc a Janssen Pharmaceutical Company; July 2022.
- Remodulin (treprostinil) Injection, for subcutaneous or intravenous use. Package Insert. United Therapeutics Corp.; July 2021.
- Orenitram (treprostinil) extended-release tablets, for oral use. Package Insert. United Therapeutics Corp.; May 2021.

Slide 8, 9, 10, 11, 12, 13

- Klinger JR, Elliott CG, Levine DJ, et al. Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report. *Chest*. 2019;155(3):565-586. doi:https://dx.doi.org/10.1016/j.chest.2018.11.030 Accessed 20190117//. Available at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med16&NEWS=N&AN=30660783
- Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *European Heart Journal*. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237 Accessed 11/21/2022. Available at https://doi.org/10.1093/eurheartj/ehac237

Points for Consideration for the Development of Prior Authorization

Failed PAH drugs	*Consider substituting "trialed" for "failed" and a clarification note to describe that marking a drug as trialed will not on its own preclude coverage for the drug (eg, for use in alternative combination regimens)*
Additional FDA-approved indications and off-label uses	*Consider accounting for all FDA-approved indications of Tyvaso DPI (treprostinil) and riociguat.* *Additionally, there are off-label uses guideline recommended and indexed in pharmacy compendia*