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APPROVED THERAPIES FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION IN ADULTS

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ABBREVIATIONS

6MWD	6-minute walking distance
ABG	Arterial blood gas
ACCP	American College of Chest Physicians
BNP	Brain natriuretic peptide
CCB	Calcium channel blocker
cGMP	Cyclic guanosine monophosphate
CHD	Congenital heart disease
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CTD	Connective tissue disease
CTEPH	Chronic thrombo-embolic pulmonary hypertension
DLCO	Lung diffusion capacity for carbon monoxide
DPAH	Drug- or toxin-associated pulmonary arterial hypertension
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HIV	Human immunodeficiency virus
HPAH	Heritable pulmonary arterial hypertension
IPAH	Idiopathic pulmonary arterial hypertension
IV	Intravenous
mPAP	Mean pulmonary artery pressure
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA-FC	New York Heart Association Functional Class
PA	Prior authorization
PAH	Pulmonary arterial hypertension
PAH-CTD	Pulmonary arterial hypertension associated with connective tissue disease

PAH-HIV	Pulmonary arterial hypertension associated with human immunodeficiency virus
PAWP	Pulmonary arterial wedge pressure
PCH	Pulmonary capillary haemangiomatosis
PDE5i	Phosphodiesterase type-5
PFTs	Pulmonary function tests
PH	Pulmonary hypertension
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
RA	Right atrium
SC	Subcutaneous
sGC	Soluble guanylate cyclase
WHO-FC	World Health Organization Functional Class
WU	Woods units

1.0 INTRODUCTION

Pulmonary arterial hypertension (PAH) is a type of pulmonary hypertension (PH) that is due to diseased pulmonary arteries. PAH leads to dysfunction and eventually failure of the right ventricle (RV). Patients with PAH have a very poor prognosis (ie, high risk of mortality) if not promptly treated.[1] Because PAH is a rare and complex life-threatening disease, ideally, patients should be treated at a center that specializes in managing PH.

Pharmacologic agents approved by the US Food and Drug Administration (FDA) for the treatment of PAH include prostacyclin pathway agonists, endothelin receptor antagonists, and nitric oxide-cyclic guanosine monophosphate enhancers, as listed in **Table 1**. These agents are referred to as PAH-specific therapies because they help ameliorate elevated pressure/resistance in the pulmonary arterial vasculature, though they do not necessarily treat underlying causes of PAH pathology.

This report focuses on the pharmacologic treatment of adults with PAH and, in particular, guideline recommendations regarding PAH-specific therapies from 2 recent guidelines: 1) the 2019 American College of Chest Physicians (ACCP) PAH guideline, and 2) the 2022 PH guideline by the European Society of Cardiology and the European Respiratory Society (ESC/ERS). We also reviewed the Utah Medicaid prior authorization (PA) form (last updated June 2022) currently in place for PAH agents. Based on guideline recommendations, potential modifications to the PA criteria and points for consideration are provided at the end of this report (Section 7.0).

Table 1. Active Ingredients FDA-Approved for the Treatment of Pulmonary Arterial Hypertension

Prostacyclin pathway agonists	Endothelin receptor antagonists	Nitric oxide-soluble guanylate cyclase- cyclic guanosine monophosphate (NO-sGC-cGMP) pathway enhancers
epoprostenol iloprost treprostinil selexipag	ambrisentan bosentan macitentan	sildenafil tadalafil riociguat

2.0 METHODS

In order to identify recent guidelines for the treatment of PAH, we searched the following websites, as well as performed a literature search in Ovid Medline* up to November 15, 2022:

- CHEST, which houses guidelines published by the American College of Chest Physicians (ACCP): https://www.chestnet.org/Guidelines-and-Topic-Collections

* Search string executed: (*Hypertension, Pulmonary/ or (pulmonary adj3 hypertension).ti.) and ((guide* or recommend* or position or consensus or standard* or practice-parameter* or treatment-algorithm).ti,pt,kw,kf. or (guideline or practice guideline or consensus development conference).pt.)

- The American Thoracic Society: https://www.thoracic.org/statements/pulmonary-vascular.php
- Lexicomp, which typically includes a link to applicable clinical guidelines within drug monographs: https://online.lexi.com/

Two guidelines stood out as the most up-to-date and pertinent for PAH-specific drug therapy: the 2019 ACCP 2019 PAH guideline[1] and the 2022 PH guideline by the ESC/ERS.[2]

We also compiled the approved indications for PAH-specific drugs and labeled warning/precaution information. Package inserts were obtained from the FDA's approved drugs database (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm) and from sponsor websites dedicated to the particular drug products, in December 2022.

The following areas related to PAH management are beyond the scope of this report: genetic testing/consultation, palliative care, supportive care, and screening for PAH. Additionally, this report does not exhaustively review other FDA-approved indications for the agents listed in Table 1.

3.0 DISEASE OVERVIEW

Pulmonary arterial hypertension (PAH) is a rare, subset condition among a heterogeneous group of pulmonary hypertensive disorders.[2] PAH corresponds to pulmonary hypertension that stems from vasculopathy of the pulmonary arteries.[2] Pulmonary hypertension causes elevated right ventricular (RV) pressures (ie, overload).[2] Chronic right ventricular overload gives rise to progressive right ventricular remodeling, dysfunction, and ultimately RV failure. Patients with PAH have a high risk of mortality.[2]

General symptoms of pulmonary hypertension include dyspnea on exertion, fatigue, weakness, palpitations, nausea, dizziness, and lightheadedness. Progressive symptoms include edema, ascites, abdominal distention, hemoptysis, and arrhythmias. Additional signs may include cyanosis, enlarged jugular veins, tachycardia, and pleural effusion.[2] RV overload and dysfunction are typically detectable by echocardiography.

The pathology in PAH consists of vascular remodeling (cell proliferation, fibrosis, constrictive lesions [medial hypertrophy, intimal and adventitial thickening], and complex lesions), inordinate vasoconstriction, and microthrombosis of the small pulmonary arteries.[3-5] Such abnormalities contribute to vessel narrowing and increased vascular resistance, hence pulmonary hypertension. "Pathologic findings include hyperplasia and hypertrophy of all three layers of the vascular wall (intima, media, adventitia) in pulmonary arteries <50 microns..."[4] Endothelial dysfunction plays a role in vasoconstriction; impaired endothelial cell production of vasodilators (eg, nitric oxide and prostacyclin) has been observed in pathophysiologic studies along with overproduction of vasoconstrictors (eg, endothelin-1).[3] Inflammatory mediators may also play a role in particular etiologies such as PAH associated with systemic sclerosis[6], connective tissue diseases, human immunodeficiency virus infection (HIV), and systemic lupus erythematosus.[3]

3.1 Classification of Pulmonary Hypertension (PH) and Pulmonary Arterial Hypertension (PAH)

PAH is classified as Group 1 pulmonary hypertension (PH) among 5 possible PH groups (as shown in **Appendix A**). Classification groupings are based on similar pathophysiological etiologies and clinical/hemodynamic presentation, therefore involving a similar intragroup treatment approach. Updates to the PH classification system, following the 6th World Symposium on Pulmonary Hypertension (WSPH) Convention in 2019, have been implemented in the most updated PAH treatment guideline[2]. The 5 main subcategories of Group 1 PH (ie, PAH) are as follows[2,7]:

Group 1 PH: Pulmonary Arterial Hypertension (PAH)

- *Idiopathic PAH (**IPAH**)*: includes vasoreactive responders and non-responders
- *Heritable PAH (**HPAH**):* genetic mutations, often bone morphogenetic protein receptor type II (BMPR2) mutations, causing PAH
- *PAH associated with*
    - drugs (**DPAH**; eg, dasatinib, leflunomide, sofosbuvir, indirubin, methamphetamines) and toxins
    - connective tissue disease (**PAH-CTD**)
    - HIV infection (**PAH-HIV**)
    - portal hypertension (**PAH-PoPH**)
    - congenital heart disease
    - schistosomiasis
- *PAH with features of venous/capillary involvement:* pulmonary venoocclusive disease, and/or pulmonary capillary hemangiomatosis
- *Persistent PH of the newborn*

Based on patient registries in countries *without* endemic schistosomiasis, idiopathic PAH (IPAH) is typically the most common subtype of PAH, followed by PAH associated with connective tissue disease (PAH-CTD), congenital heart disease, portal hypertension PAH (PAH-PoPH), and drugs/toxins (DPAH).[2,8] Based on a variety of national registry studies (many more than 10 years old) idiopathic PAH (IPAH) and heritable PAH (HPAH) were estimated to occur in about 5 to 15 per one million adults.[4,9] The incidence of PAH overall has been reported in several European registries to be between 5 to 52 cases per million persons.[4] Recent data for the US incidence of PAH and various PAH subclasses is unavailable.

3.2 Hemodynamic Parameters Applicable to PAH

The hemodynamic parameters to define PH have changed over the years. In 2019, international experts published revised hemodynamic definitions for PH following the convention of the 6th WSPH.[7] PAH is characterized by pre-capillary PH (as are some other forms of PH). Pre-capillary PH is defined as the concomitant presence of mean pulmonary arterial pressure (mPAP) >20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) ≥3 Woods units (WU).[7] The 2022 European Society of Cardiology and the European Respiratory Society (2022) guideline uses the same mPAP and PAWP parameter cutoffs for pre-capillary PH, however, uses PVR>2 WU rather than >3 WU because there is evidence of increased mortality between 2-3 WU.[10]

3.3 Diagnosis Overview

Patients with suspected PAH or RV dysfunction seen on echocardiography should be promptly referred to and evaluated at PH centers of expertise, if possible.[1,2] The diagnosis and management of PAH requires multidisciplinary input and coordinated care from a variety of specialists (eg, cardiologists, pulmonologists, rheumatologists, radiologists, cardiothoracic surgeons), but ideally should include a specialist with experience in managing PAH.[1] Care should be coordinated between the PH specialist and the patient's general physicians, as any potential contributing causes of PAH should be aggressively treated.[1] Prompt referral and coordination of therapy allows earlier diagnosis and initiation of therapy, and overall, improved outcomes.[2]

PH is typically detected by echocardiography abnormalities; chest radiography abnormalities may also lead to suspicion of PH. The ESC/ERS advises that upon the suspicion of PH, further evaluation should include forced spirometry, body plethysmography, lung diffusion capacity for carbon monoxide (DLCO), and arterial blood gas (ABG) assessments, which aid in distinguishing between the different clinical subtypes of PH. In PAH, pulmonary function tests (PFTs) may be normal or may reveal mild restrictive and/or obstructive abnormalities; however, patients with PAH associated with congenital heart disease (CHD) typically have more severe PFT abnormalities. DLCO may be normal or reduced in PAH. Arterial blood gas (ABG) oxygen (ie, PaO2) is typically normal or slightly reduced, and PaCO2 typically reduced, in PAH.[2] Notably, patients should be referred promptly to PH centers of expertise in the following scenarios[2]:

a) If there are warning signs or risk factors for PAH (eg, rapid progression of symptoms [ie to World Health Organization Functional Classification III/IV], severely reduced exercise capacity, pre-syncope or syncope on mild exertion, signs of right heart failure and/or low cardiac output, poorly tolerated arrhythmias, hypotension/tachycardia). The ESC/ERS states that warning signs warrant immediate intervention.
b) When PAH or CTEPH (chronic thrombo-embolic pulmonary hypertension) are suspected
c) When the patient has intermediate or high echocardiographic probability of PH

Altogether, the aforementioned assessments help screen for possible PH and eventually help differentiate the PH subtype; but, a right heart catheterization (RHC) assessment for PAWP and mPAP must be conducted to confirm a diagnosis of PAH. Right heart catheterization is the gold standard for diagnosing PAH, and requires a highly trained specialist to perform the procedure correctly, and to interpret the findings in the context of the entire clinical picture including other diagnostic and laboratory investigations.[1,2] However, not all patients can undergo a RHC. Contraindications include known thrombus or tumor in the right ventricle or atria; recently implanted (<1 month) pacemaker, mechanical right heart valve, TriClip, and acute infection. Nonetheless, the risk/benefit should be individually assessed and discussed with the patient to decide if RHC should be withheld. A serious risk of the RHC procedure is perforation of a pulmonary artery.[2] Newly diagnosed cases of PH/PAH undergo further analyses to identify comorbidities and possible causes or complications.

The ESC/ERS describes obtaining the following laboratory tests in establishing the diagnosis.

Assessments upon suspicion of PH (Step 1)

- blood pressure, heart rate, and pulse oximetry

- blood test to determine brain natriuretic peptide (BNP)/ N-terminal pro-brain natriuretic peptide (NT-proBNP)
- resting electrocardiogram
- complete medical history and physical exam

Assessments to detect PH: non-invasive lung and cardiac testing (Step 2)

- echocardiography: recommended as a diagnostic investigation when PH is suspected (Level B evidence[†]). Tricuspid regurgitation velocity > 2.8 m/s in presence of other EKG signs suggestive of PH is used to assign probability of PH
- cardiopulmonary exercise testing
- PFTs with DLCO are recommended as initial assessment in patients with PH
- Chest computed tomography imaging should be considered in the work up of PH and may help detect CTEPH
- Ventilation/perfusion, perfusion lung scan may also help detect CTEPH
- ABG, Chest X-ray may help rule out other lung disease

Invasive testing and assessment of comorbidities (Step 3)

- Right heart catheterization for indicated patients, ideally to be carried out in PH centers of expertise[‡]
- Vasoreactive testing by catheterization for indicated patients (see Section 5.1) ideally to be carried out in PH centers of expertise
    - It is imperative that vasoreactivity testing is performed and interpreted by providers with appropriate training and experience as there are risks of adverse events and misinterpretations that could lead to inappropriate application of calcium channel blockers (CCBs).
- Routine biochemistry, hematology, immunology, HIV testing, and thyroid function are recommended in patients with PAH to help identify potential associated etiologies
    - blood counts (including hemoglobin)
    - serum electrolytes (sodium, potassium)
    - kidney function (creatinine, glomerular filtration rate, and urea)
    - uric acid
    - liver parameters (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, γ-glutamyl transpeptidase, bilirubin)
    - iron status (serum iron, transferrin saturation, and ferritin)
    - BNP or NT-proBNP
    - Serological studies for hepatitis viruses and HIV infections
    - Immunology laboratory work-up including anti-nuclear antibodies, anti-centromere antibodies, and anti-Ro

[†] Data is based on a single RCT or large non-randomized studies

[‡] PH centers of expertise, according to the ESC/ERS guidelines and the European Reference Network on rare respiratory diseases, were considered to assess at least 200 patients per year with at least 100 resulting in a diagnosis of PAH. Additionally the center should ideally be actively managing 50 patients with PAH or CTEPH and have at least two new referrals per month with PAH or CTEPH. However, authors described that these patient thresholds can be adapted according to specific country characteristics but ideally low-volume centers should develop collaboration relationships with high-volume centers.

    - Thyroid function (thyroid-stimulating hormone), since PAH can be associated with thyroid disorders
- Abdominal ultrasound is recommended to screen for portal hypertension
- Ventilation/perfusion lung scan (planar or single-photon emission computed tomography) for patients with suspected or newly diagnosed PH to detect possible CTEPH which may occur in 7–10% of patients with PAH or pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangiomatosis (PCH).[2]

3.4 Disease Severity

PAH disease severity assessment encompasses not just a single parameter, but rather should take into consideration multiple parameters. The ACCP guideline advises that at the least the following parameters should be considered to assess disease severity and therapeutic decisions: the World Health Organization Functional Classification (WHO-FC), exercise capacity assessment, echocardiography, laboratory (eg, brain natriuretic peptide levels), and hemodynamic assessments.

The ACCP specifies therapy recommendations primarily according the WHO-FC status of the patient's condition but also includes consideration of markers for poor clinical prognosis and clinical goals. The WHO-FC status is a strong predictor of survival at diagnosis and follow-up visits.[2] Worsening WHO-FC is an indicator of disease progression which should be urgently addressed. The WHO-FC classes are as follows[1,2]:

- **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.

The ESC/ERS guideline also supports assessing disease severity by multi-parameter assessment but goes a step further and endorses using risk stratification (ie, the estimated 1 year mortality prognosis of the patient based on multi-parameter assessment) to guide therapy decision making.[2] The risk strata, which also incorporate WHO-FC, are described further in Section 5.2.2. The treatment goal expressed by the ESC/ERS guideline is to achieve and maintain a low-risk profile.[2] Guideline recommendations for pharmacotherapy regimens from each of these guidelines (2019 ACCP, 2022 ESC/ERS) are expanded upon in Section 5.0.

4.0 PAH-SPECIFIC THERAPIES

Treatments for PAH generally include off-label use of high-dose calcium channel blockers (CCBs), application of agents approved for PAH, combination regimens, and possibly eventual lung transplantation. In this report, drugs that are FDA-approved for PAH will be referred to as "PAH drugs" or "PAH-specific" pharmacotherapies. Drug-therapy decision-making is based on evaluation of the patient's disease severity, the risk for short-term deterioration, patient/provider preferences, and patient-specific goals.[1]

Agents that are FDA-approved for PAH target the following physiologic pathways:

1. The prostacyclin pathway
    - Endogenous prostacyclin stimulates vasodilation.[11] In PAH, the prostacyclin pathway is thought to be disrupted; subnormal levels of prostacyclin synthase have been observed in the pulmonary arteries of patients with PAH, in addition to reduced prostacyclin urinary metabolites.[2,12,13] The therapeutic prostacyclin analogues (eg, **epoprostenol, iloprost, treprostinil**) and prostacyclin receptor agonists (eg, **selexipag**) induce vasodilation, inhibit platelet aggregation, and have cytoprotective and anti-proliferative activities.[2]
2. The endothelin pathway
    - Therapeutic endothelin receptor antagonists (ERAs; eg, **ambrisentan, bosentan, and macitentan**) antagonize the vasoconstriction and proliferation effects of endogenous endothelin-I (ET-1) in the smooth muscles of the pulmonary arteries. In PAH, ET-1 is upregulated and mediates deleterious effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation.[3,14] Elevated concentrations of ET-1 have been observed in the plasma and lung tissue of patients with PAH. Elevated plasma ET-1 concentrations are also correlated with elevated mean right atrial pressure and disease severity in patients with PAH.[15]
3. The nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate (NO-sGC-cGMP) pathway
    - Therapeutic agents in this category increase cGMP, a mediator of vasodilation in pulmonary vascular smooth muscles. PAH is associated with "…impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle."[16] Therapeutic mechanisms-of-action that increase cGMP include stimulating soluble guanylate cyclase (sGC) activity to catalyze cCMP synthesis (as with **riociguat**), or inhibiting the breakdown of cGMG through phosphodiesterase-5 (PDE5; as with **sildenafil and tadalafil**).

Table 2 outlines the mechanism of action for the PAH-specific pharmacotherapies, organized by drug class.

Table 2. Mechanism of Action of PAH Drugs

Active Ingredient	Labeled Mechanism of Action
Prostacyclin Analogs	
Epoprostenol	Direct vasodilator of pulmonary and systemic arterial vasculature and an inhibitor of platelet aggregation[11]
Iloprost	Vasodilator of pulmonary and systemic arterial vasculature. Also has platelet aggregation inhibitory effect, but the relevance to PAH efficacy is unknown[17]
Treprostinil	Direct vasodilator of pulmonary and systemic arterial vasculature. Also has platelet aggregation inhibitory effect[18]
Prostacyclin Receptor Agonist	
Selexipag	Selective prostacyclin IP receptor agonist activity reduces pulmonary vascular resistance and increases cardiac index. Although this agent inhibits platelet aggregation in-vitro, there is was no effect on platelet parameters for in vivo studies at doses used for PAH.[19]
Endothelin Receptor Antagonists	
Ambrisentan	Blocks endothelin receptor subtype ET_A (to a much greater degree than ET_B), and leads to vasodilation[15]
Bosentan	Blocks endothelin receptors on endothelium and vascular smooth muscle (slightly more selective for ET_A than ET_B), and leads to vasodilation[20]
Macitentan	Blocks endothelin (ET)-1 from binding to endothelin receptor subtypes ET_A and ET_B.[14] In PAH, the endothelin system is upregulated and associated with vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. Blockade of this system yields clinical benefits in PAH.[14]
Phosphodiesterase Type-5 Inhibitors	
Sildenafil	Inhibits PDE5 degradation of cGMP in smooth muscles of pulmonary vasculature. This increases cGMP and results in relaxation of pulmonary vascular smooth muscles.[16,21]
Tadalafil	
Soluble Guanylate Cyclase Stimulator	
Riociguat	Directly stimulates sGC and also stabilizes nitric oxide binding to soluble sGC enzyme. Both actions increase the synthesis of cGMP. Increasing cGMP produces vasodilation.[22]

Abbreviations: cGMP, cyclic guanosine monophosphate; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase-5; sGC, soluble guanylate cyclase

4.1 Labeled Indications of Agents Approved for the Treatment of PAH

Each of the reviewed PAH drugs is labeled for the treatment of PAH (ie, WHO Group 1 PH) for a variety of clinical objectives, as listed below:

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
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 a composite 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

Refer to **Table 3** for the labeled indication for each formulation, as well as information regarding the study population of initial clinical trials, as stated in package inserts.

The labeled indications are not specific to age, with the exception of sildenafil (Revatio; approved specifically for adults) and bosentan (Tracleer; indicated for patients with PAH as young as 3 years of age). The remaining agents listed in **Table 3** have not been established in the pediatric population *according to package inserts*. Nonetheless, several PAH-drugs are recommended for off-label use in pediatric PAH[23]; this topic will be reviewed further in a separate report.

Two products have additional indications for other types of PH aside from PAH:

- Riociguat has an indication for persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH; WHO PH Group 4).
- Treprostinil inhalation dosage forms (solution and dry powder for inhalation) are approved for pulmonary hypertension associated with interstitial lung disease (WHO PH Group 3), to improve exercise ability[18,24]

Table 3. PAH Products, Labeled Indications, and PAH Clinical Trial Population

Active Ingredient Brands	Labeled Indications	Pivotal Clinical Trial Adult Study Population with PAH
Prostacyclin Analogs		
Epoprostenol Flolan 0.5 mg for reconstitution Veletri 0.5 mg for reconstitution; **Generic available**	*IV infusion*: approved for the treatment of PAH, to improve exercise capacity[11,25]	Pivotal clinical trials mainly included patients with **NYHA-FC III-IV** symptoms (97%) and idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%)[11]
Iloprost Ventavis 10 or 20mcg/mL solution	*Inhalation*: approved for the treatment of PAH, to improve the composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.[17]	Pivotal clinical trials mainly included patients with **NYHA-FC III-IV** symptoms and idiopathic or heritable PAH subtypes (65%) or PAH associated with connective tissue diseases (23%)[17]
Treprostinil Remodulin solution for injection: 20 to 200 mg/20 mL; **Generic available** Tyvaso DPI powder for Inhalation: 16 to 48 mcg dosage units Tyvaso solution for inhalation: 0.6mg/mL Orenitram ER tablet: 0.125 mg to 5 mg dosage units	*Injection (SC or IV):* approved for the treatment of PAH, to decrease exercise-associated symptoms, or to reduce the rate of clinical deterioration when transitioning from epoprostenol[26] *Inhalation:* approved for the treatment of 1. PAH, to improve exercise ability[18] 2. PH associated with interstitial lung disease (WHO PH Group 3), to improve exercise ability[18] *Oral:* approved for the treatment of PAH, to delay disease progression and to improve exercise capacity[27]	Pivotal clinical trials with the injection formulation included patients with **NYHA-FC II-IV** and idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%)[26] Pivotal clinical trials with the inhalation formulation mainly included patients with **NYHA-FC III** symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%)[18] Pivotal clinical trials with the oral formulation included mainly patients with **WHO-FC II-III** symptoms and idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%)[27]
Prostacyclin Receptor Agonist		
Selexipag Uptravi 1800 mcg for reconstitution for IV use; Uptravi tablets, 200 to 1800 mcg/tablet	*Oral and IV:* approved to delay disease progression and reduce the risk of hospitalization for PAH[19]	Long-term pivotal study included patients with **WHO-FC II-III** and etiologies of idiopathic or heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%)[19]

Table 3. PAH Products, Labeled Indications, and PAH Clinical Trial Population

Endothelin Receptor Antagonists		
Ambrisentan Letairis 5 mg and 10mg tablet; **Generic available**	*Oral:* approved for PAH to improve exercise ability and delay clinical worsening. Also approved in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.[15]	Pivotal clinical trials predominantly included patients with **WHO FC II–III** symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%)[15]
Bosentan Tracleer 62.5 mg and 125 mg tablets; **Generic available** Tracleer soluble 32mg tablet for oral suspension	*Oral:* approved for the treatment of 1. PAH in adults with WHO-FC II, III, or IV to improve exercise ability and to decrease clinical deterioration[20] 2. Approved for PAH in pediatric patients ≥3 years with idiopathic or congenital PAH to improve pulmonary vascular resistance[20]	Pivotal clinical trials mainly included patients with **WHO FC II-IV** symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%)[20]
Macitentan Opsumit 10 mg tablet	*Oral:* approved for the treatment of PAH to reduce risks of disease progression and hospitalization[14]	The long-term pivotal clinical study in PAH mainly included patients with **WHO-FC II-III**, treated for about 2 years, and etiologies of idiopathic or heritable PAH (57%), or PAH associated with connective tissue disorders (31%) or congenital heart disease with repaired shunts (8%)[14]
Phosphodiesterase Type-5 Inhibitors		
Sildenafil Revatio 10mg/12 mL IV solution; **Generic available** Revatio 10 mg/mL oral suspension; **Generic available** Revatio 20mg tablet; **Generic available**	*Oral or IV injection:* approved for the treatment of PAH in **adults** to improve exercise ability and delay clinical worsening[21]	Pivotal clinical trials mainly included PHA of **NYHA-FC II – III** symptoms, etiologies of idiopathic PAH (71%) or PAH associated with connective tissue disease (25%)[20,21]
Tadalafil Tadliq 20mg/5 mL oral suspension Adcirca 20 mg tablet Alyq 20 mg tablet	*Oral:* approved for the treatment of PAH to improve exercise ability[16,28,29]	Pivotal clinical trials mainly included patients with **NYHA-FC II – III** symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%)[16,28,29]

Table 3. PAH Products, Labeled Indications, and PAH Clinical Trial Population

Soluble Guanylate Cyclase Stimulator		
Riociguat Adempas 0.5 mg to 2.5 mg tablets	*Oral:* approved for the treatment of 1. PAH to improve exercise capacity, improve WHO-FC and to delay clinical worsening[22] 2. Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH; WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO-FC[22]	Riociguat was studied as monotherapy or in combination with ERAs or prostanoids. Pivotal clinical trials mainly included patients with **WHO-FC II–III** and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%)[22]

Abbreviations: DPI, dry powder for inhalation; ER, extended release; IV, intravenous; ERAs, endothelin receptor antagonists, NYHA-FC, New York Heart Association Functional Class; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WHO-FC, World Health Organization Functional Class

4.2 Labeled Warnings and Precautions

The warnings and precautions for all classes of PAH-specific drugs are provided in **Table 4**, along with clinically relevant drug interactions, as reported in the product labeling.

Table 4. Warnings and Precautions for PAH Therapies

Prostacyclin Analogs
Epoprostenol[11,25]
Contraindications • Congestive heart failure due to severe left ventricular systolic dysfunction • Pulmonary edema during dose initiation: avoid use if this occurs (labeled for Veletri brand product) • Hypersensitivity to the drug or to structurally related compounds Warnings • Do not abruptly lower the dose or withdraw dosing due to the potential for rebound pulmonary hypertension, which can be life-threatening. • The patient should be closely monitored upon initiation and dose changes in a setting with personnel and equipment for physiologic monitoring and emergency care. • A permanent indwelling central venous catheter plus anticoagulation are indicated for continuous long-term administration of this therapy. Drug interactions • Additive hypotensive effect with diuretics, antihypertensive agents, or other vasodilators; use with caution • Antiplatelet agents or anticoagulants plus epoprostenol may theoretically increase the risk of bleeding, though this adverse effect was not observed in clinical trials. • Epoprostenol increases digoxin exposure; monitor levels closely

Table 4. Warnings and Precautions for PAH Therapies

Iloprost[17]
Contraindications: None Warnings • Hypotension leading to syncope has been observed (aside from exertional syncope associated with PAH). Do not initiate therapy in patients with systolic blood pressure below 85 mmHg. The patient should be closely monitored upon initiation of therapy • Discontinue if pulmonary edema is present, since this may be a sign of pulmonary venous hypertension • May cause bronchospasm. Caution is advised for patients with history of hyper-reactive airway disease • *Specific Populations*: Advised not to breastfeed while taking iloprost Drug interactions • Has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents • Potential for increased risk of bleeding in patients on anticoagulants or platelet inhibitors
Treprostinil[18,26,27]
Contraindication • Severe hepatic impairment (labeled for Orenitram formulation only) Warnings • May cause symptomatic hypotension, particularly in patients with low systemic arterial pressure (labeled for the IV and inhalation forms) • Inhibits platelet aggregation, and therefore may increase the risk of bleeding (labeled for the IV and inhalation forms) • The inhalation dosage form may cause bronchospasm. Caution is advised for patients with history of hyper-reactive airway disease • Do not abruptly lower or stop the intravenous dose because this results in worsening symptoms • For intravenous continuous infusion, continuous subcutaneous infusion is the preferred delivery mode versus using an indwelling central venous catheter with an external infusion pump; the latter is associated with a higher risk of blood stream infections and sepsis. • Titrate the intravenous formulation slowly in patients with hepatic insufficiency • In patients with diverticulosis, tablet formulation can become lodged in a diverticulum. Drug interaction • Dosage adjustments should be considered when inhibitors or inducers of CYP2C8 are added or withdrawn
Prostacyclin Receptor Agonist
Selexipag[19]
Contraindications • Use with strong CYP2C8 inhibitors (eg, gemfibrozil) • Hypersensitivity to the active substance or to any of the product excipients Warnings • If signs of pulmonary edema occur, consider possible pulmonary veno-occlusive disease; and if confirmed, discontinue treatment. • *Specific Populations*: o Advised not to breastfeed o Avoid use in severe hepatic impairment Drug interactions • Moderate CYP2C8 inhibitors (eg, clopidogrel) increase exposure; reduce the dose. • CYP2C8 inducers (eg, rifampin) decrease exposure; increase the dose.

Table 4. Warnings and Precautions for PAH Therapies

Endothelin Receptor Antagonists
Drug Class Warnings
• Embryo-fetal toxicity **Black Box Warning**: Use is contraindicated during pregnancy. A REMS program is in place for female patients • Peripheral edema is a class effect of ERAs and a symptom of PAH; depending on the edema severity, patients may require intervention with a diuretic, fluid management, hospitalization for decompensating heart failure, and/or a change in PAH therapy. • If signs of pulmonary edema occur, consider possible pulmonary veno-occlusive disease, and if confirmed, discontinue treatment. • ERAs may decrease sperm count; caution patients • May decrease hemoglobin within the first few weeks. Measure hemoglobin at initiation, at 1 month, and periodically thereafter • May cause elevated liver enzymes, and/or hepatotoxicity/liver failure (**Black Box Warning** for bosentan; warning for other ERAs). Monitor liver enzymes at baseline and as clinically indicated. • Breastfeeding not advised while taking ERAs
Ambrisentan[15]
Additional contraindications • Idiopathic pulmonary fibrosis Additional warnings • *Special populations*: Not recommended in moderate or severe hepatic impairment Drug interaction • Cyclosporine increases ambrisentan exposure; reduce the dose.
Bosentan[20]
Additional contraindications • Use with cyclosporine or glyburide • Hypersensitivity to the active substance or to any of the product excipients Drug interactions • Drugs metabolized by CYP2C9 and CYP3A can increase exposure to bosentan and/or the co-administered drug • Bosentan decreases hormonal contraceptive exposure and reduces effectiveness
Macitentan[14]
• Additional contraindications: Hypersensitivity to the active substance or to any of the product excipients • Drug interactions: o Avoid use of strong CYP3A4 inducers (eg, rifampin) o Avoid use of strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir) o Avoid use of moderate dual CYP3A4 and CYP2C9 inhibitors (eg, fluconazole, amiodarone) or use of combined CYP3A4 and CYP2C9 inhibitors

Table 4. Warnings and Precautions for PAH Therapies

Phosphodiesterase Type-5 Inhibitors
Drug Class Warnings
Contraindications • Use with organic nitrates or riociguat • Hypersensitivity to the active substance or to any of the product excipients Warnings • Hypotension is a possible side effect and may be more common in patients with resting hypotension or on antihypertensive therapy • Use in pulmonary veno-occlusive disease may cause pulmonary edema and is not recommended • Seek immediate medical care if sudden hearing or visual impairment occur. Although a causal effect is unclear, PDE5 inhibitors appear associated with hearing impairment and non-arteritic anterior ischemic optic neuropathy (NAION). Reported cases are rare and many are associated with risk factors. • Caution regarding risk of priapism • Avoid use with other PDE5 inhibitors
Sildenafil[21]
Additional Warnings • Chronic use in pediatric patients is not recommended due to increased mortality observed in a long-term clinical trial with increasing doses of sildenafil • Epistaxis occurred in 13% of patients with PAH-CTD in clinical trials. Caution is advised in such patients. • Vaso-occlusive crises were more common in patients with PH secondary to sickle cell disease treated with sildenafil versus placebo. The effectiveness/safety of sildenafil in PAH due to sickle cell disease is not established. Drug interactions • Avoid use with ritonavir and other potent CYP3A inhibitors • Use caution and monitor blood pressure when used with other blood pressure lowering agents (eg, alpha blockers, amlodipine)
Tadalafil[29]
Additional Warnings • Avoid use in severe renal or hepatic impairment; reduce dose in mild/moderate renal or hepatic impairment
Soluble Guanylate Cyclase Stimulator
Riociguat[22]
Contraindications • Pregnancy: **Black Box Warning** for possible fetal harm; REMS program is in place for females of reproductive potential to ensure non-pregnancy status • Use with nitrates or nitric oxide donors • Use with phosphodiesterase inhibitors • Use with other soluble guanylate cyclase stimulators • Pulmonary hypertension associated with idiopathic interstitial pneumonias Warnings • Symptomatic hypotension possible especially in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or taking antihypertensives or strong CYP and P-gp/BCRP inhibitors (eg, ketoconazole, protease inhibitors)

Table 4. Warnings and Precautions for PAH Therapies

- Bleeding: in placebo controlled trials serious bleeding occurred in 2.4% of treated patients vs. 0% of placebo treated patients.
- If signs of pulmonary edema occur, consider possible pulmonary veno-occlusive disease, and if confirmed, discontinue treatment.
- Specific Populations:
  - Advised not to breastfeed while taking riociguat
  - Avoid use in severe renal or hepatic impairment
  - Smoking: may require higher doses in smokers

Abbreviations: cGMP, cyclic guanosine monophosphate; CYP, cytochrome P450 enzyme; ERAs, endothelin receptor antagonists; IV, intravenous; NAION, non-arteritic anterior ischemic optic neuropathy; PDE, phosphodiesterase; PAH-CTD, pulmonary arterial hypertension associated with connective tissue disease; REMS, Risk Evaluation and Mitigation Strategy

5.0 GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF PAH

5.1 High-Dose Calcium Channel Blockers (CCBs)

A small subset of patients with PAH (about 10-20%)[30] are expected to benefit from off-label use of high-dose CCB therapy (eg, long-acting nifedipine or diltiazem, or amlodipine). In order to establish candidacy for high-dose CCB therapy, indicated patients undergo vasoreactivity testing via heart catheterization (with inhaled nitric oxide, iloprost, or IV epoprostenol) to determine if they may benefit from CCBs.[2] Factors increasing the risk of adverse events during vasoreactivity testing include having WHO-FC IV symptoms, low systemic BP, low CO, or PVOD.[1] In these cases, patients who are not candidates for vasoreactive testing would likewise not be candidates for high-dose CCBs.

The most updated clinical guideline (2022 ESC/ERS) for PAH recommends vasoreactivity testing only for certain subtypes of PAH (IPAH, HPAH, or DPAH); testing patients outside of these subtypes is specifically recommended against (Class III, Level C [§]).[2]

The 2019 ACCP guideline *suggested considering* CCB therapy for vasoreactive patients with PAH, in the absence of right-sided heart failure or contraindications to CCBs (rated as an ungraded consensus-based suggestion). This rating means that supportive evidence for CCB therapy was inadequate to make a graded recommendation and the clinical benefit/safety of CCBs was uncertain. Authors also highlighted that evidence for CCBs may not extend to all circumstances of vasoreactive PAH. For instance, there was a lack of studies to support CCB use in PAH due to connective tissue disorders (PAH-CTD).[1] The newer 2022 ESC/ERS guideline specifies the PAH subgroups most likely to benefit from CCB therapy, recommending high-dose CCB therapy only for vasoreactive IPAH, HPAH, or DPAH subsets. The ESC/ERS guideline also rated the evidence supporting CCB therapy as low-level evidence (ie, based on expert consensus opinion and/or small studies, retrospective studies, or registries).[2]

Considering that CCBs are off-label for PAH, a provider must use their clinical judgement to determine if the therapy is in the patient's best interest. They must weigh the risks of vasoreactivity testing and the patient's candidacy for CCB therapy. The provider and/or patient may favor PAH-approved therapies, especially in scenarios where there is limited or no evidence supporting CCBs for the patient's specific PAH subgroup. CCBs should not be used for 1) empiric treatment of PAH (ie, in absence of a positive vasoreactive result), 2) PAH that is non-vasoreactive, 3) in the presence of right ventricular failure, or 4) when there are contraindications to CCBs.[1] Patients who are not candidates for CCBs or who have inadequate response to CCBs should initiate PAH-approved therapy as further described in the following sections.

According to the ESC/ERS guideline, a positive response to CCB therapy is an improvement in WHO-FC, achieving class I or II, with considerable hemodynamic improvement (mPAP <30 mmHg and PVR <4 WU), and BNP <50 ng/L or NT-proBNP <300 ng/L.[2]

[§] Class III: Evidence or general agreement that the procedure is not useful or may be harmful; Level C: Based on expert consensus of opinion and/or small studies, retrospective studies, or registries.

5.2 PAH Dugs Recommended in Recent Clinical Guidelines

5.2.1 2019 ACCP Guideline

At the time of the ACCP committee's evidence review, there was insufficient evidence to recommend for or against the use of selexipag or oral treprostinil. Thus, in this section regarding the 2019 ACCP recommendations, "prostanoid therapy" will refer to the following agents in particular: epoprostenol, iloprost, and injectable and inhalable treprostinil. Notably, the 2022 ESC/ERS guideline includes recommendations for selexipag and oral treprostinil, as described in the following section.

The 2019 ACCP guideline specifies therapy recommendations according to WHO-FC presentation and specifies treatment modifications based on clinical worsening and WHO-FC at follow-up.[1]

For *initial therapy* in patients with symptomatic PAH presenting as **WHO-FC II or III** who are not candidates for CCBs or who have failed CCBs, the ACCP (2019) suggests using a combination of **ambrisentan and tadalafil** to improve 6 minute walk distance (6MWD) (weak recommendation, moderate quality evidence).[1] For patients unable to tolerate this combination, monotherapy with an FDA-approved PAH drug (ie, an ERA, PDE5 inhibitor, or sGC stimulator) should be considered. The PAH agent is chosen based on the priority therapy goal of patient/provider: improving 6MWD, improving WHO-FC, and/or delaying the time to clinical worsening, based on clinical trial evidence for the differing endpoints.[1] See **Table 5** for details regarding the specific agent(s) suggested per WHO-FC status (ie, clinical scenario) at initiation and outcome goal.

Initial therapy with parenteral prostanoid therapy is suggested for PAH presenting with **WHO-FC III** and evidence of rapidly progressing disease or markers for a poor clinical prognosis.[1] In patients who initiated therapy with one or two oral PAH agents but who present with WHO-FC III symptoms and evidence of progression and/or markers of poor clinical prognosis at follow-up, *add-on therapy* with a parenteral or inhaled prostanoid is suggested. Prostanoid therapy is typically reserved for later-in-line therapy for PAH presenting with WHO-FC II.[1]

PAH with **WHO-FC IV** carries a high risk of mortality; moreover, data is lacking or very limited to support the use/efficacy of *oral* therapies for PAH in this population. Prostanoid therapy, either as parenteral or inhaled, is preferred over oral therapies for PAH with WHO-FC IV. Lung transplantation should be considered and discussed with patients in WHO-FC IV, or those in WHO-FC III despite use of optimized pharmacotherapy.

For PAH with **WHO-FC III or IV** and unacceptable clinical status despite receiving a PAH-specific monotherapy, addition of a second class of PAH therapy to improve exercise capacity is advised. For those with unacceptable or deteriorating clinical status despite two classes of PAH pharmacotherapy, addition of a third class of PAH therapy is suggested. Ideally, patients who require combination therapy should be managed at centers with expertise in PH.

Table 5. 2019 American College of Chest Physicians Guideline Recommendations for PAH-specific Therapies

- At the time of the evidence review, the panel found insufficient evidence to recommend for or against the use of selexipag or oral treprostinil.

Symptomatic Patients with PAH

- CCBs should **not** be used empirically to treat PAH in the absence of a positive vasoreactive result (Ungraded consensus-based statement)
- In patients with connective tissue diseases and vasoreactivity, authors described a lack of studies supporting CCB therapy in this subpopulation
- In the absence of right-sided heart failure or contraindications to CCBs, patients with PAH and acute vasoreactivity should be considered for a trial of an oral CCB (Ungraded consensus-based statement)
  - Long-acting nifedipine or diltiazem, or amlodipine are suggested.
    - Effective doses in IPAH are 120–240 mg for nifedipine, 240–720 mg for diltiazem; and up to 20 mg for amlodipine.
    - Verapamil should be avoided (due to its negative inotropic effects)
  - Initial reassessment should occur after 3 months on therapy.
  - Additional or alternative treatment should be considered if the patient has not achieved WHO-FC class I or II

Patients with WHO-FC II Symptoms

- For treatment-naive patients with PAH presenting with WHO-FC II symptoms who are not candidates for CCBs, or who have failed CCB therapy, a combination of **ambrisentan and tadalafil** should be initiated to improve 6MWD (weak recommendation, moderate quality evidence)
  - For patients who are unwilling or unable to tolerate combination therapy, an approved ERA, PDE5i, or riociguat should be considered for initiation
    - **ambrisentan** is recommended to improve 6MWD (strong recommendation, low quality evidence)
    - **bosentan** is suggested to delay the time to clinical worsening (Ungraded Consensus-Based Statement)
    - **macitentan** is suggested to delay the time to clinical worsening (Ungraded Consensus-Based Statement)
    - **sildenafil** is recommended to improve 6MWD (strong recommendation, low quality evidence)
    - **tadalafil** is suggested to improve 6MWD (Ungraded Consensus-Based Statement)
    - **riociguat** to is suggested to improve 6MWD, improve WHO-FC, and delay the time to clinical worsening (Ungraded Consensus-Based Statement)
  - Parenteral or inhaled prostanoids should not be used as initial therapy for treatment-naive patients with WHO-FC II, or as second-line agents for PAH patients with WHO-FC II (Ungraded Consensus-Based Statement)

Patients with WHO-FC III Symptoms

- For treatment-naive patients with PAH and WHO-FC III symptoms who are not candidates for CCBs, or who have failed CCB therapy, a combination of **ambrisentan and tadalafil** should be initiated to improve 6MWD (weak recommendation, moderate quality evidence)
  - For those unwilling or unable to tolerate combination therapy, monotherapy with an approved an ERA, PDE5i, or riociguat is advised:
    - **ambrisentan** is recommended to improve 6MWD (strong recommendation, low quality evidence)
    - **bosentan** is recommended to improve 6MWD (strong recommendation, moderate quality evidence)
    - **bosentan** is suggested to decrease PAH-related hospitalization in the short-term (weak recommendation, low quality evidence)

Table 5. 2019 American College of Chest Physicians Guideline Recommendations for PAH-specific Therapies

- **macitentan** is suggested to improve WHO-FC and to delay the time to clinical worsening (Ungraded Consensus-Based Statement)
- **sildenafil** is recommended to improve 6MWD (strong recommendation, low quality evidence), and to improve WHO-FC (Ungraded Consensus-Based Statement)
- **tadalafil** is suggested to improve 6MWD, to improve WHO-FC, and to delay time to clinical worsening (Ungraded Consensus-Based Statement)
- **riociguat** to is suggested to improve 6MWD, improve WHO-FC, and to delay the time to clinical worsening (Ungraded Consensus-Based Statement)

- For those with unacceptable clinical status despite established PAH-drug monotherapy, addition of a second class of PAH therapy is suggested to improve exercise capacity. Refer to *Additional Combination Regimens* below.
- **Add-on prostanoid therapy**:
  - If symptoms persist and/or evidence of disease progression despite stable/appropriate doses of 1 or 2 oral agents, the addition of the following prostanoids should be considered:
    - **inhaled treprostinil** is suggested to improve 6MWD/exercise capacity after inadequate response to an ESA or PDE5i (weak recommendation, low quality evidence)
    - **inhaled iloprost** is suggested to improve WHO-FC, delay the time to clinical worsening, and to improve 6MWD/exercise capacity, after inadequate response to an ESA or PDE5i (Ungraded Consensus-Based Statement)
    - **IV epoprostenol** is suggested to improve WHO-FC and to improve 6MWD, after inadequate response to 1 or 2 oral agents (Ungraded Consensus-Based Statement)
    - **IV treprostinil** is suggested to improve 6MWD, after inadequate response to 1 or 2 oral agents (Ungraded Consensus-Based Statement)
- Initial treatment with a parenteral prostanoid should be considered for treatment naive PAH with WHO-FC III and evidence of rapid progression of disease or markers of a poor clinical prognosis
  - **IV epoprostenol** is suggested to improve WHO-FC and to improve 6MWD (Ungraded Consensus-Based Statement)
  - continuous **IV treprostinil** is suggested to improve 6MWD (Ungraded Consensus-Based Statement)
  - continuous **subcutaneous treprostinil** is suggested to improve 6MWD (Ungraded Consensus- Based Statement)

Patients With WHO-FC IV Symptoms

- Initial **parenteral prostanoid** therapy is suggested for treatment-naive PAH with WHO-FC IV
  - continuous **IV epoprostenol** is suggested to improve WHO-FC and to improve 6MWD (Ungraded Consensus-Based Statement)
  - **IV treprostinil** is suggested to improve 6MWD (Ungraded Consensus-Based Statement)
  - continuous **subcutaneous treprostinil** is suggested to improve 6MWD (Ungraded Consensus-Based Statement)
- If patients are unable to or do not wish to undergo parenteral prostanoid therapy, an **inhaled prostanoid** in combination with an oral PDE5i and an ERA is suggested (Ungraded Consensus-Based Statement).
- For those with unacceptable clinical status despite established PAH-drug monotherapy, addition of a second class of PAH therapy is suggested to improve exercise capacity. Refer to *Additional Combination Regimens* below.

Additional Combination Regimens Recommended to Improve Exercise Capacity for Patients with WHO-FC III or IV and Unacceptable Clinical Status, despite PAH-specific Monotherapy

- In patients remaining symptomatic on stable doses of an ERA or a PDE5i, addition of **inhaled iloprost** is suggested to improve 6MWD (Ungraded Consensus-Based Statement).

Table 5. 2019 American College of Chest Physicians Guideline Recommendations for PAH-specific Therapies

- If symptoms persist on stable doses of established IV epoprostenol, addition of **sildenafil** or up titration of **epoprostenol** is suggested to improve 6MWD (Ungraded Consensus-Based Statement)
- In patients remaining symptomatic on stable doses of bosentan, ambrisentan or an inhaled prostanoid, addition of **riociguat** is suggested to improve 6MWD, WHO-FC, and to delay the time to clinical worsening (Ungraded Consensus-Based Statement)
- In patients remaining symptomatic on stable doses of a PDE5i or an inhaled prostanoid, **macitentan** is suggested to improve 6MWD, WHO-FC, and to delay the time to clinical worsening (Ungraded Consensus-Based Statement)
- For those with unacceptable or deteriorating clinical status despite two classes of PAH pharmacotherapy, addition of **a third class of PAH therapy** is suggested (Ungraded Consensus-Based Statement).
- For stable or symptomatic PAH patients on ambrisentan, add-on **tadalafil** can be considered to improve 6MWD (weak recommendation, low quality evidence)

Abbreviations: 6MWD, 6 minute walking distance; CCBs, calcium channel blockers; ERA, endothelin receptor antagonist; IV, intravenous; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase-5 inhibitor; WHO-FC, World Health Organization functional class

Grading system:

- *Strong recommendation, moderate quality evidence: Benefits clearly outweigh risks for most cases; moderate confidence in the effect estimate, but higher-quality research may impact the estimate and recommendation*
- *Strong recommendation, low quality evidence: Benefits clearly outweigh risks for many cases; however, confidence in the effect estimate is limited and higher-quality research may impact the estimate and recommendation*
- *Weak recommendation, low quality evidence: There is uncertainty in the estimates of benefits/risks (may be closely balanced), and confidence in the effect estimate is limited; other alternatives may be equally reasonable*
- *Ungraded Consensus-Based Statement: expert opinion that benefits outweigh risk; insufficient evidence for a graded recommendation*

5.2.2 2022 ESC/ERS Guideline

The 2022 ESC/ERS guideline on PH recommends using mortality risk-assessment tools to guide PAH-specific therapy initiation and modifications at follow-up. A 3-strata risk tool is used to guide initial PAH treatment; whereas, a 4-strata risk tool is used for therapy decision-making at follow-up (see **Table 6**). Achieving and maintaining low risk of poor prognosis is the main objective of treatment; lower risk status "…is usually associated with good exercise capacity, good quality of life, good RV function and a low mortality risk," (page 85).[31] Patients with PAH require regular follow-up, with risk stratification assessment, and inquiry of patient adherence to therapy.

Table 6. Risk Assessment Tools Used for Therapy Decision Making in the ESC/ERS 2022 Guideline

3 Strata Risk Tool for Initial Therapy Decision-making			
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 to 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%
4 Strata Risk Tool for Therapy Decision-making at Follow-up[a]			
	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

Table 6. Risk Assessment Tools Used for Therapy Decision Making in the ESC/ERS 2022 Guideline

Abbreviations: 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; ESC/ERS, European Society of Cardiology/European Respiratory Society; 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.

[a] *Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.*

Initial therapy is based on a) the PAH subtype; b) a comprehensive risk assessment including the strongest predictive parameters for mortality in PAH (WHO-FC, 6MWD, and BNP/NT-proBNP) and other informative parameters, as shown in Table 6; c) whether the patient has cardiopulmonary comorbidities; and d) whether the patient is a candidate for vasoreactive testing and CCB therapy. Authors state that the PAH-CTD subtype should be treated according to the same treatment algorithm as for IPAH. Recommendations that follow pertain to patients who are either inappropriate for vasoreactive testing, non-vasoreactive, or for patients who had inadequate response to CCB therapy. Refer to Section 5.1 for guideline recommendations on CCB therapy.

Initial PAH-drug therapy for patients with IPAH, HPAH, DPAH, or PAH-CTD (in any mortality risk category) ***with*** *cardiopulmonary* comorbidities is conservative, starting with PDE5i or ERA monotherapy. Cardiopulmonary comorbidities include risk factors for left ventricular diastolic dysfunction, such as obesity, diabetes, coronary heart disease, a history of hypertension, and/or a low lung diffusion capacity for carbon monoxide. If at follow-up these patients (with PAH and cardiopulmonary comorbidities) present at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, additional PAH medications may be considered on an individual basis. Similar to patients with cardiopulmonary comorbidities, patients with PAH associated with portal hypertension or HIV are generally to be treated with monotherapy first, followed by sequential therapy if needed.

For patients with IPAH, HPAH, DPAH, or PAH-CTD who present **without** cardiopulmonary comorbidities and high risk of death (or at intermediate risk of death plus severe hemodynamic impairment), initial triple therapy with a PDE5i, an ERA, and an injectable prostacyclin analog is recommended for consideration. For those presenting at low or intermediate risk of death without cardiopulmonary comorbidities, initial dual therapy with an ERA and PDE5i is recommended. Escalation in therapy is advised (ie, addition of a prostacyclin and/or referral for a lung transplant) is recommended if at follow-up the patient is at intermediate-high or high risk of death. Addition of selexipag, or a switch from PDE5i therapy to riociguat, is recommended for consideration at follow-up in patients at intermediate-low risk of death, to reduce the risk of clinical worsening. Initial combination therapy is also used for patients with PAH after corrected adult CHD, with injectable prostacyclin analogues considered for those at high risk. Recommendations regarding the specific combinations or sequence of additive agents are further delineated in **Table 7,** which summarizes the 2022 ESC/ERS recommendations for PAH-specific therapy.

Table 7. 2022 European Society of Cardiology and the European Respiratory Society (ESC/ERS) PAH Guideline

- Guideline recommendations[a] do not supersede the clinical judgement/responsibility of the health professional to make appropriate treatment decisions respective to the patient's unique health conditions
- Off-label use may be recommended when there is sufficient evidence supporting that the recommended therapy could be considered medically appropriate, that the patient may benefit from the recommended therapy, and when it is in the patient's best interest. However, off-label use of a medication should commence only after obtaining consent from the patient.
- **Right heart catheterization (RHC)** is recommended to confirm the diagnosis of PH (especially PAH or CTEPH) and to support treatment decisions (Class I, Level B). RHC should be performed in experienced centers (Class I, Level C)
- **Vasoreactivity testing** is recommended in IPAH, HPAH, and DPAH to detect those who can be treated with a high dose CCB (Class I, Level B). This test is not recommended for other forms of PAH (Class III, Level B); and should be performed at centers of expertise in PH (Class I, Level C). A positive vasoreactivity testing result is considered as a reduction in mPAP≥10 mmHg to reach an absolute value of mPAP≤40 mmHg with an increased or unchanged CO (Class I, Level C).
- The overarching treatment goal is to achieve and maintain a low-risk profile on optimized medical therapy (Class I, Level B); In some PAH etiologies and comorbidities, optimization of therapy should be considered on an individual basis while acknowledging that a low-risk profile is not always achievable (Class IIa)
- A three-strata model (low, intermediate, and high risk) is recommended for use at the time of PAH diagnosis, taking into account all available clinical/laboratory data (Class I, Level B)
- A four-strata model (low, intermediate–low, intermediate–high, and high risk) is recommended for risk stratification a follow-up based on WHO-FC, 6MWD, and BNP/NT-proBNP, with other variables taken into account as necessary (Class I, Level B)

A. Calcium Channel Blockers (CCBs): For <u>vasoreactive</u> idiopathic, heritable, or drug-associated PAH

- **High dose CCB therapy is recommended in patients with IPAH, HPAH, or DPAH who are responders to acute vasoreactivity testing** (Class I,C)
  - Follow-up with complete reassessment after 3–4 months is recommended
  - Continue high dose CCB in patients with IPAH, HPAH, and DPAH who achieved WHO-FC I or II with hemodynamic improvement (mPAP<30 mmHg and PVR <4 WU) (Class I, Level C). Initiate PAH therapy for patients with continued WHO-FC III or IV or without marked hemodynamic improvement despite the use of high doses of CCBs. (Class I,C)
  - The guideline algorithm (Figure 8 in the guideline) also implies that a positive response to CCB therapy includes attaining WHO-FC I/II, BNP <50 ng/L or NT-proBNP <300 ng/L, and normal or near-normal resting hemodynamics. Patients are indicated for other PAH-specific drugs if any of these markers are unsatisfactory with CCB therapy.
  - "In patients with a positive vasoreactivity test but insufficient long-term response to CCBs who require additional PAH therapy, continuation of CCB therapy should be considered." (Class IIa, C), (page 3664, Table 7)
- "CCBs are **not recommended** in patients **without a vasoreactivity study or non-responders**, unless prescribed for other indications (e.g. Raynaud's phenomenon)." (Class III, C), (page 3664, Table 7)
- Target doses for CCBs for PAH
  - Amlodipine 15-30 mg QD; Diltiazem 120-360 mg BID; Felodipine 15-30 mg QD; Nifedipine 20-60 mg BID or TID

Table 7. 2022 European Society of Cardiology and the European Respiratory Society (ESC/ERS) PAH Guideline

The following recommendations can be applied to patients who are either non-vasoreactive, inappropriate for vasoreactivity testing/CCBs, or had insufficient response to CCB therapy

B. For patients with IPAH, HPAH, DPAH, or CTD-associated PAH[b] who present without cardiopulmonary comorbidities[c]

Initial Therapy

- For those presenting at high risk of death, or at intermediate risk of death with severe hemodynamic impairment, initial **triple combination therapy** with PDE5i, an ERA, and an injectable prostacyclin analogue should be considered. (Class IIa, Level C)
- For patients presenting at low or intermediate risk of death, initial combination therapy with an **ERA and a PDE5i** is recommended. (Class I, Level B)
  - "Although the quality of evidence is low, initial oral combination therapy with an ERA and a PDE5i achieves important targets in symptom improvement (functional class), exercise capacity, cardiac biomarkers, and reduction of hospitalizations." (page 3668)
- Initial oral combination regimens recommended include the following: **ambrisentan plus tadalafil** (Class I, Level B), and **macitentan plus tadalafil** (Class I, Level B). Other combinations of ERA and PDE5i may be considered (Class IIa, Level B). However, selexipag should not be added to macitentan/tadalafil for initial therapy (Class III, Level C).

Follow-up Therapy

- For patients achieving a low-risk status with their initial PAH therapy, continuation of treatment is recommended.
- For those presenting at intermediate–low risk of death at follow-up while receiving ERA/PDE5i therapy, the addition of **selexipag** should be considered (Class IIa, Level C), to reduce the risk of clinical worsening.
- For those presenting at intermediate–low risk of death while receiving ERA/PDE5i therapy, switching from PDE5i to **riociguat** may also be considered (Class IIb, Level B)
- For those at intermediate–high or high risk while receiving oral therapies, the addition of **IV epoprostenol** or **injectable treprostinil** and referral for lung transplant evaluation should be considered.
  - If adding injectable prostacyclin analogues is unfeasible, adding **selexipag** or switching from PDE5i to **riociguat** may be considered.

C. Sequential Drug Combination Options for patients with IPAH, HPAH, DPAH, or CTD-associated PAH[b] who present without cardiopulmonary comorbidities[c]

- The following sequential drug combinations (ie, escalation of therapy) can be considered to reduce the risk of morbidity/mortality events:
  - **macitentan** added to **PDE5i** or **oral/inhaled prostacyclin** analogues (Class I, Level B)
  - **selexipag** added to **ERAs** and/or **PDE5i** (Class I, Level B)
  - **oral treprostinil** added to ERA or PDE5i/**riociguat** (Class I, Level B)
- bosentan plus sildenafil is not recommended to reduce the risk of morbidity/mortality (Class III, Level B)
- The following sequential drug combinations (ie, escalation of therapy) can be considered to improve exercise capacity**:**
  - **sildenafil** added to **epoprostenol** (Class I, Level B)
  - **treprostinil** added to **sildenafil** or **bosentan** (Class IIa, Level B)
  - **riociguat** added to **bosentan** (Class IIa, Level B)
  - **tadalafil** added to **bosentan** (Class IIb, Level C)
  - **inhaled iloprost** added to **bosentan** (Class IIb, Level B)
  - **ambrisentan** added to **sildenafil** (Class IIb, Level C)

Table 7. 2022 European Society of Cardiology and the European Respiratory Society (ESC/ERS) PAH Guideline

- **bosentan** added to **sildenafil** (Class IIb, Level C)
- **sildenafil** added to **bosentan** (Class IIb, Level C)
- **Other** sequential double- or triple-combination therapies may be considered to improve exercise capacity and/or alleviate pulmonary hypertension symptoms (Class IIb, Level C)

- The combination of riociguat and PDE5i is not recommended (Class III, Level B)

D. For patients with IPAH, HPAH, DPAH, or CTD-associated PAH[b] who present with cardiopulmonary comorbidities[c]

- Consider initiating monotherapy with a PDE5i or an ERA (Class IIa, Level C)
- In those presenting at intermediate or high risk of death while receiving PDE5i or ERA monotherapy, additional PAH medication may be considered on an individual basis (Class IIb, Level C)

E. PAH Subsets, Additional Considerations

- **PAH-CTD** should be treated by the same treatment algorithm as for IPAH. (Class I, Level C)
- Consider treating **PAH-HIV** with initial PAH-drug monotherapy, followed by sequential combination if needed, taking into consideration comorbidities and drug–drug interactions (Class IIa, Level C)
- **PAH-PoPH** "…should follow the same general principles as in other patients with PAH, taking into account the severity of underlying liver disease, the indication for liver transplantation, and the potential effects of PAH medication on gas exchange, which may deteriorate with vasodilators in patients with PoPH," (page 3677). Monotherapy with PAH drugs, followed by sequential combination if necessary, should be considered (Class IIa, Level C).
- **PAH associated with congenital heart disease**:
  - Consider employing ERAs, PDE5i, riociguat, prostacyclin analogues, and prostacyclin receptor agonists (Class IIa, Level C): sequential combination therapy should be considered if patients do not meet treatment goals (Class IIa, Level C)
  - bosentan is recommended in symptomatic patients with Eisenmenger syndrome to improve exercise capacity (Class I, Level B)
  - "In patients with PAH after corrected adult CHD, initial oral combination therapy with drugs approved for PAH should be considered for patients at low and intermediate risk, while initial combination therapy including i.v./s.c. prostacyclin analogues should be considered for patients at high risk" (Class IIa, Level C), (page 3680, Table 19)
- **PAH with signs of venous/capillary involvement (PVOD/PCH)**
  - In patients with PVOD/PCH, the use of drugs approved for PAH may be considered with careful monitoring of clinical symptoms and gas exchange (Class IIb, Level C)

Abbreviations: 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; BID, twice daily; CCB, calcium channel blocker; CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; ERA, endothelin receptor antagonist; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PCH, pulmonary capillary hemangiomatosis; PDE5i, phosphodiesterase 5 inhibitor(s); PoPH, portal hypertension, PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; QD, once daily; sGC, soluble guanylate cyclase; TID, three times daily; WHO-FC, World Health Organization functional class; WU, Wood units.

Table 7. 2022 European Society of Cardiology and the European Respiratory Society (ESC/ERS) PAH Guideline

[a] **Class of recommendation**: Class I, the treatment is recommended; Class II, there is conflicting evidence and/or divergence of expert opinions about the usefulness/efficacy of the treatment; Class IIa, the treatment should be considered; Class IIb, the treatment may be considered; Class III, the treatment is not recommended
Level of evidence: A, data is based on multiple RCTs or meta-analyses; B, data is based on a single RCT or large non-randomized studies; C, consensus expert opinion and/or small studies, retrospective studies, or registry data
[b] Authors advise treating CTD-PAH in the same manner as IPAH (per Figure 9, and in recommendation table 15)
[c] Cardiopulmonary comorbidities include risk factors for HFpEF such as obesity, diabetes, coronary heart disease, a history of hypertension, and/or a low lung diffusion capacity for carbon monoxide

5.2.3 Other Uses for PAH Drugs

Although a full review of other forms of PH is beyond the scope of this report, below are ESC/ERS guideline recommendations regarding PAH drugs for use in other PH types (eg, WHO PH group 3 or 4).

- Consider inhaled treprostinil in patients with PH associated with interstitial lung disease (ILD), WHO group 3 PH, (Class IIb, B).[2]
- "Riociguat is recommended for symptomatic patients with inoperable CTEPH [WHO group 4 PH] or persistent/recurrent PH after PEA [pulmonary endarterectomy]," (Class I, B; page, 3698, Table 24A).[2]
- "Treprostinil [subcutaneous] may be considered in patients in WHO-FC III–IV who have inoperable CTEPH or persistent/recurrent PH after PEA," (Class IIb, C; page, 3698, Table 24A).[2]
- "Off-label use of drugs approved for PAH may be considered in symptomatic patients who have inoperable CTEPH" (Class IIb, B; page, 3698, Table 24A).[2] In such patients, combined therapy with sGC stimulator/PDE5i, ERA, or parenteral prostacyclin analogues may be considered (Class IIb, C).[2]
- "No recommendation can be given for or against the use of PDE5is in patients with HFpEF [WHO group 2 PH] and combined post- and pre-capillary PH," (page 3690, Table 22 A).[2]

As mentioned in Section 4.1, riociguat and inhalation treprostinil have FDA-approved indications for WHO PH group 3 and 4, respectively (ie, non-PAH indications):

- Treprostinil inhalation dosage forms (solution and dry powder for inhalation) are approved for PH associated with interstitial lung disease (WHO PH Group 3), to improve exercise ability[18,24]
- Riociguat has an indication for persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4).[22]

Table 8 compiles PAH drug uses indexed in Micromedex as an "effective" or "possibly effective" non-FDA use; and uses indexed in Lexicomp as an off-label use. Notably, Lexicomp documents some uses that are guideline recommended (denoted as level of evidence [LOE] G, in blue color), as follows:

- Use in vasoreactive testing in pulmonary hypertension (for epoprostenol and iloprost): Though Lexicomp cites the older 2015 ESC/ERS guideline, this recommendations was retained in the updated 2022 ESC/ERS guideline.[2] It may be that Lexicomp reviewers have not yet reviewed the

updated guideline, as additional off-label uses are included in the guideline for other agents (eg, to treat WHO PH group 4) as previously mentioned above.[2]

- Use for digital ulcers in systemic sclerosis (for bosentan)[32]
- High altitude pulmonary edema (for sildenafil)[33]
- Raynaud's phenomenon (for sildenafil)[32]

The following agents had **no** off-label uses listed as "effective" or "evidence favors efficacy" in Micromedex, nor any off-label uses stated in Lexicomp: ambrisentan, macitentan, selexipag, treprostinil, and riociguat.

Table 8. Off-Label Uses of PAH-Drugs

Micromedex[a,34]	Lexicomp[b,35]
Epoprostenol	
Effective (Category B): • Vasoreactivity testing in pulmonary hypertension • Angina pectoris *Evidence favors efficacy (Category B):* • Hemodialysis • Operation on heart with cardiopulmonary bypass with pulmonary hypertension • Transplant of kidney pretreatment *Evidence favors efficacy (based on case report):* • Eisenmenger's syndrome	• Vasoreactivity testing in pulmonary hypertension **(LOE G)** • Refractory, moderate-severe acute respiratory distress syndrome (LOE C) • Heart surgery complicated by pulmonary hypertension, right ventricular dysfunction, or refractory hypoxemia (LOE B)
Iloprost	
Evidence favors efficacy (Category B): • Acute kidney injury following administration of contrast media, prophylaxis • Transient osteoporosis	• Vasoreactivity test in pulmonary hypertension **(LOE C, G)**
Bosentan	
Evidence favors efficacy (Category B) • Eisenmenger's syndrome, WHO FC III pulmonary arterial hypertension	• Digital ulcers in systemic sclerosis **(LOE B, G)** • Raynaud phenomenon in systemic sclerosis (LOE C)
Sildenafil	
Evidence favors efficacy • Persistent pulmonary hypertension of the newborn (Category B) • Secondary Raynaud's phenomenon (Category B) • Drug withdrawal, Nitric oxide (adults/pediatric case reports) • Erectile dysfunction: various therapy-induced or disease-induced etiologies listed (see Micromedex)	• High altitude pulmonary edema **(LOE G)** • Raynaud's phenomenon **(LOE B, G)**
Tadalafil	
Evidence favors efficacy • Secondary Raynaud's phenomenon (Category B)	• High altitude pulmonary edema **(LOE G)**

Abbreviations: LOE, level of evidence; RCTs, randomized controlled trials

Table 8. Off-Label Uses of PAH-Drugs

[a] Non-FDA uses were extracted from Micromedex that were rated as "effective" or "evidence favors efficacy"; note that some off-label uses are viewable in the "In-depth Answers" view but not in the "Quick Answers" view of the database.

Micromedex Category B strength of evidence is based on data from meta-analyses of RCTs with either incongruent effect estimates, small populations, significant methodological flaws, or nonrandomized studies.

[b] All listed off-label uses are specified for the adult population

LexiComp Level of Evidence Definitions:

- *B - Evidence from RCT(s) with important limitations, or very strong evidence of some other research design. Estimate of effect may change with future evidence.*
- *C - Evidence from observational studies, unsystematic clinical experience, or from potentially flawed. Estimate of effect is uncertain.*
- *G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.*

6.0 UTILIZATION DATA

Table 9 shows 2022 pharmacy utilization data for agents approved for PAH, within the Utah Medicaid Fee-for-service (FFS) adult population. Over the 1 year period, there were 24 adults who utilized a PAH drug of interest (127 total claims). Generic sildenafil comprised 37% of total claim counts, followed by generic tadalafil (26%), Opsumit (macitentan, 21%), ambrisentan (primarily as Letairis, 11%), and the remaining as <5% (Tyvaso [treprostinil] inhalation, Uptravi [selexipag] tablets). No pharmacy claims were found for epoprostenol, iloprost, bosentan, or riociguat in the adult population.

Table 9. 2022 Medicaid Fee-for-service Pharmacy Claims, Adults

Active Ingredient	Product	Patients	Claims
Ambrisentan	AMBRISENTAN TAB 10MG	<5	<5
Ambrisentan	LETAIRIS TAB 10MG	<5	10
Ambrisentan	LETAIRIS TAB 5MG	<5	<5
Macitentan	OPSUMIT TAB 10MG	5	27
Selexipag	UPTRAVI TAB 1600MCG	<5	<5
Selexipag	UPTRAVI TAB 200MCG	<5	<5
Selexipag	UPTRAVI TAB 600MCG	<5	<5
Selexipag	UPTRAVI TAB 800MCG	<5	<5
Sildenafil Citrate	SILDENAFIL TAB 20MG (Pulmonary Hypertension)[a]	10	47
Tadalafil	TADALAFIL TAB 5MG	<5	11
Tadalafil	TADALAFIL TAB 20MG (Pulmonary Hypertension)[a]	5	22
Treprostinil	TYVASO REFIL SOL 0.6MG/ML	<5	<5
Total		**24**	**127**

[a] *Products are indexed as pulmonary hypertension formulations in the claims database—to differentiate those for erectile dysfunction*

Regarding medical claims, there were less than 5 adult patients receiving a PAH drug through medical billing in 2022. The 15 total medical claims for PAH drugs in 2022 consisted of Remodulin injection (treprostinil; as 10 claims, or 67% of the total medical claims), and less than 5 claims each for Opsumit (macitentan) 10 mg tablet, and sildenafil 20 mg tablet.

7.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION (PA) CRITERIA

This section will refer to the current Utah Medicaid Pulmonary Arterial Hypertension prior authorization (PA) form (June 2022 version, uploaded September 2022), and includes suggestions for possible clarifications or modifications where applicable. The current Medicaid PA form pertains to the following agents and includes PA criteria listed A through G below:

- ***Nitric Oxide-cGMP Enhancers***: Adcirca (tadalafil), Adempas (riociguat), Alyq (tadalafil), Revatio (sildenafil)
  - Note that Tadliq (tadalafil) is not listed on the current PA form but can be incorporated.
- ***Prostacyclin-related therapies***: Flolan (epoprostenol), Veletri (epoprostenol), Ventavis (iloprost), Orenitram (treprostinil), Remodulin (treprostinil), Tyvaso (treprostinil), Uptravi (selexipag)
- ***Endothelin receptor antagonists***: Letairis (ambrisentan), Tracleer (bosentan), Opsumit (macitentan)

Agents with preferred status on the Utah Medicaid Preferred Drug List (January 2023 version) include generic tadalafil, generic sildenafil, generic epoprostenol, generic ambrisentan, and Tracleer (brand for bosentan).

A. *The PA form requires prescribing of PAH therapy to be by or in consultation with a pulmonologist or cardiologist:*
   - Recent guidelines recommend that it is ideal for patients with diagnosed or suspected PAH to be referred to and managed by PH specialists at specialty PH centers[**], since these providers will be most experienced in managing this rare and complex disease. The ACCP 2019 guideline elaborates that "…most physicians, including those whose subspecialty practice includes pulmonary and cardiology, are unlikely to encounter sufficient numbers of patients with PAH to gain meaningful experience with the diagnosis and management of this disease," (page 579).[1] However, it is unclear if such PH centers are accessible to *all* Utah Medicaid fee-for-service patients; thus, having the broader allowance for pulmonologists/cardiologists in general to engage in prescribing may offer greater accesses/flexibility to patients while aiming to ensure prescribing is decided by a provider with expertise in cardiopulmonary diagnoses and decision-making.

B. *Requirement to meet PAH indication:* In order to receive any of the agents included on the PA form, patients must have a diagnosis of PAH, with confirmation by a right heart catheterization in adults and documentation of mean PAP (mPAP).
   - Right heart catheterization (RHC) is the gold standard to obtain accurate hemodynamic measurements (eg, cardiac output, PAWP) to confirm PAH. Nonetheless, ESC/ERS guideline authors describe that, "Although haemodynamics represent the central element of characterizing PH, the final diagnosis and classification should reflect the whole clinical context and consider the results of all investigations," (page 3636).[2] Group 1 PH (ie, PAH) is characterized by pre-capillary

[**] The Pulmonary Hypertension Association (PHA) accredits PH centers of expertise in the US; the list of accredited centers can be found at https://phassociation.org/phcarecenters/accredited-centers/. Two centers are listed for Utah: The Chronic Thromboembolic Pulmonary Hypertension (CTEPH) program at Intermountain Medical Center (Murray, UT), and Pulmonary Hypertension Program University of Utah Health (Salt Lake City, UT).

PH, defined as mPAP >20 mmHg, PAWP ≤15 mmHg, and PVR >2 WU or >3 WU (depending on the guideline).[2,7] However, there may be some flexibility in these thresholds, as guideline authors state, "…any PAWP threshold is arbitrary and that the patient phenotype, risk factors, and echocardiographic findings, including left atrial (LA) volume, need to be considered when distinguishing pre- from post-capillary PH," (page 3637).[2] Additionally, contraindications to RHC (eg, mechanical right heart valve, TriClip, presence of thrombus/tumor in right ventricle or atria, or recent right pacemaker placement) or scenarios where performing the procedure is considered too risky, may prevent patients from receiving the procedure temporarily or permanently.[2]

- Medical necessity may be considered in cases where RHC is contraindicated. For example, prescribers could state clinical rationale with other supportive laboratory findings, plus consultation with a provider at a PH center of expertise if applicable.

- The PA form requires documentation of mPAP. For patients submitting the PA form who have been receiving PAH therapy, it is not clear if the PA form is requiring documentation of the patient's current mPAP or a historical mPAP. mPAP can improve with PAH treatment, thus, requiring a certain *current* mPAP for treatment-experienced patients could impede continuation of treatment for maintaining the patient in stable condition (eg, improved hemodynamic condition). Moreover, a repeat RHC is not absolutely clinically indicated at the initiation of each new PAH drug or at every 6 month follow-up visit.

***PA Clarification**: If a likeness of this criterion is maintained, the following wording may be considered to clarify which mPAP measurement the form is requesting and consider cases that cannot undergo RHC:*

*Diagnosis of pulmonary arterial hypertension, confirmed in adults by right heart catheterization. Indicate the patient's **historical** mean PAP (prior to PAH treatment) to support the PAH diagnosis. Or, if the patient is unable to undergo RHC, state reason and, if provider is not with a PH specialty center, attest to consultation with PH specialty center to support PAH diagnosis.*

- Agents listed on the PA form are each approved for the treatment of PAH. Two of these agents have additional FDA-approved indications aside from PAH.
  - Riociguat is also approved for the treatment of persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO PH Group 4) after surgical treatment or inoperable CTEPH, to improve exercise capacity and WHO-FC.[22] The 2022 ESC/ERS guideline recommends its use for symptomatic CTEPH with inoperable or persistent/recurrent PH after pulmonary endarterectomy.[2]
  - The inhalation formulation of treprostinil (Tyvaso DPI) is also approved for the treatment of pulmonary hypertension associated with interstitial lung disease (WHO PH Group 3), to improve exercise ability.[18] The 2022 ESC/ERS guideline recommends that it be considered for use in this population.[10]

***PA Modification**: These additional FDA-approved indications may be considered for incorporation into the PA form or in a separate drug-specific PA form. If incorporated into the current form, it should be independent of criteria designed for the PAH indication.*

- The 2022 ESC/ERS guideline includes recommendations for use (off-label in the US) of certain agents for CTEPH, a rare type of PH (WHO PH group 4) which may or may not co-occur with PAH:
  - Subcutaneous treprostinil can be considered for patients with WHO-FC III–IV who have inoperable CTEPH or persistent/recurrent PH after pulmonary endarterectomy, (Class IIb, C).[2]
  - "Off-label use of drugs approved for PAH may be considered in symptomatic patients who have inoperable CTEPH," (Class IIb, B; page, 3698).[2] In such patients, combined therapy with an sGC stimulator, PDE5i, ERA, or parenteral prostacyclin analogue may be considered (Class IIb, C).[2]

- Refer to Table 8 (page 27) of this report to review off-label uses that are indexed in pharmacy compendia (Micromedex and Lexicomp) and additional uses that are noted by Lexicomp to be recommended by clinical guidelines for non-PAH indications.

***PA Modification**: May consider incorporation of space into the PA form or in a separate drug-specific PA form to allow the prescriber to express PA-submissions for therapy according to compendia-recommended diagnosis and/or latest treatment guidelines for such off-label indication.*

C. *Requirement for all patients with PAH to have vasoreactive testing*: The PA form appears to require that all patients undergo vasoreactive testing prior to receiving an FDA-approved agent for PAH. However, not all patients with PAH are candidates for vasoreactive testing and vasoreactive testing is not necessary for choosing approved PAH drugs for candidates of such therapy. In other words, patients who are not candidates for vasoreactivity testing and/or CCBs should receive therapies approved for PAH per standard of care.
   - The ESC/ERS recommends vasoreactive testing only for certain subsets of patients with PAH: those with idiopathic PAH (IPAH), heritable PAH (HPAH), or drug-associated PAH (DPAH). Authors specifically recommend against vasoreactive testing in PAH patients outside of these subgroups.[2] Furthermore, patients who are not candidates for CCBs (as further described below) should not be required to undergo vasoreactive testing.

***PA Modification**: If a likeness of this criterion on the current PA form is maintained, consider adding a field for the provider to attest that vasoreactivity testing is inappropriate for such cases. Alternatively, the criterion for vasoreactivity testing may be considered for removal.*

D. *Requirement to step through CCBs:* The PA form appears to require that all patients with PAH must fail a trial of CCB therapy prior to initiating agents approved for PAH. However, not all patients with PAH are candidates for off-label use of high-dose CCBs, and a forced trial can lead to undue harm in such patients. Examples of scenarios in which patients are not candidates for CCBs (or in which CCB therapy may be considered inappropriate per the provider's clinical judgement) include:
   - Patients who are not indicated for vasoreactive testing or who are unable to undergo vasoreactive testing

        - Empiric treatment with CCBs is recommended against (based on ACCP consensus) due to risk of harm (severe hypotension, syncope, RV failure)[2] and a lack of high-quality evidence to support empiric treatment with CCBs.[1,2]
    - Patients who have a negative vasoreactive result[1,2]
    - Patients for whom there is inadequate evidence supporting the use of CCBs for their PAH subtype.
        - For instance, the 2019 ACCP guideline stated there was no evidence to suggest that CCBs are beneficial for PAH-CTD.[1]
        - PAH subgroups other than IPAH, HPAH, and DPAH are not recommended for vasoreactive testing and thus not strongly indicated for CCBs, per the 2022 ESC/ERS guideline.[2]
    - Patients with PAH who have right ventricular (RV) failure, regardless of vasoreactivity; CCBs can cause harm in patients with RV failure.[1]
    - When there is a contraindication to CCB treatment[1]
    - When the risks are judged to be too high per the provider/patient perspective: Patients at increased risk of adverse events during vasoreactivity testing are those with WHO FC-IV symptoms, a low systemic blood pressure, low cardiac output, or pulmonary veno-occlusive disease.[1]

Guideline recommendations in favor of the use of CCB therapy in vasoreactive PAH are based on low-level evidence.[1,2] There is some uncertainty regarding the clinical benefit/safety of CCBs due to insufficient high-quality evidence.[1,2] Patients who are not candidates for CCBs should be initiated on FDA-approved PAH therapies as further described in Section 5.2 and Tables 5 and 7.

***PA Modification**: If a likeness of this criterion on the current PA form is maintained, consider adding a field for the provider to attest that CCBs are inappropriate for the patient if unable to demonstrate trial and failure of maximum tolerated doses of CCBs.*
Alternatively, since a small proportion of the PAH population is expected to benefit from CCBs (10-20%),[30] criteria related to requirement for vasoreactivity testing and CCB therapy could be considered for removal.

E. *Patient **has** WHO-FC II, III, or IV*. The existing Medicaid PA form requires patients to have PAH of WHO-FC II, III, or IV in order to receive PAH-specific medications.
    - It is not clear if patients applying for reauthorization, to continue their PAH therapy, must re-execute this criterion box; this bullet can be disregarded if they do not need to. While this criterion aligns with guideline-recommendations for treatment-naive patients, this may be misinterpreted for treatment-experienced patients (ie, during PA **re-**authorization) whose functional status is dynamic and can improve while on PAH therapy. A patient may presumably improve to **WHO-FC I** due to a positive response to PAH therapy. There is nothing in guidelines to suggest that a patient should be discontinued from beneficial PAH therapy if they improve to WHO-FC I while on therapy. Rather, the 2022 ESC/ERS guideline specifies that patients should continue with their initiated effective therapy to maintain a low-risk status.[2] PAH therapies are not curative; chronic, consistent PAH-therapy is required to maintain a lower mortality risk

status for the patient. This point should be considered when patients are submitting a PA re-authorization to continue their PAH therapy.

- It should also be considered that this criterion, as currently written, may prevent switches in PAH therapies while the patient has improved to WHO-FC I status— for example, to lessen burden of side effects/intolerability, or to transition from injectable to oral therapy once their condition has stabilized. There is nothing in the guidelines that suggests a patient must undergo intentional decompensation of function/disease control for the purposes of switching/optimizing PAH therapy.

***PA Modification**: this criterion may be considered for removal in order to ensure that patients are able to a) receive continued PAH therapy to maintain an improved clinical status which may include WHO-FC I, and to b) switch between therapies while improved to WHO-FC I for purposes of tailoring therapy to the patient's needs. Alternatively, if a likeness of this criterion is maintained, rewording may be considered to prevent miss-application to treatment-experienced patients (eg, consider changing to "Patient has **a history of** WHO-FC II, III, or IV," to not be confused with their current status).*

F. *The current PA form requires the provider to check the PAH therapies that the patient has tried and failed.* Additionally, in order for the patient to receive a PDL non-preferred product, the patient is required to trial and fail a PDL preferred product, or the prescriber must demonstrate medical necessity for a non-preferred product.

- If mono-drug therapy or dual-drug therapy is inadequate, additional medication can be added per standard of care. Thus, these "inadequate" therapies are not "failed" drugs per se, but rather the particular regimen of mono- or dual-therapy may have failed. Thus, it is unclear at what point the provider is supposed to mark a drugs as "failed" on the PA form since there may be a variety of combination regimens in which application of a particular drug may result in clinical improvement. Additionally, it is unclear what the consequence is (ie, payer's action) if a drug is checked as "failed" (eg, whether a patient can continue to receive the drug in alternative combination regimens).

***PA Clarification**: may consider omitting "and failed" and include a clarification note to describe that marking a drug as tried will not on its own preclude coverage for the drug (eg, for use in alternative combination regimens).*

- The Medicaid Preferred Drug List differentiates PAH therapies by drug class (ie, ERAs, PDE5is, and prostacyclin pathway therapies) and includes at least 1 agent as preferred in each drug-class category. Thus, it appears patients are able to initiate mono or multi-drug regimens (eg, dual therapy or triple therapy) with drugs of different mechanisms of action.

G. *Requirement for re-authorization*: The PA form requires re-authorization every 6 months for continued use of PAH drugs. There is also a requirement to demonstrate 1) medical justification with an updated letter, or 2) a positive 6-minute walk test (6MWT) or FEV1 at reauthorization.
   - Patients with PAH are expected to be on PAH therapy long-term, or life-long, since PAH drugs are not curative. Requirement for reauthorizations may unexpectedly result in sudden discontinuation or pauses in therapy (eg, if the patient has unexpected cancelations of office visits, or has difficulty/inability scheduling appointments or timely consultation by a specialist). Sudden discontinuations or pauses in therapy may result in hospitalizations due to exacerbated pulmonary hypertension. The board may consider whether re-authorizations are necessary for this chronic disease that requires consistent, long-term therapy.
   - The lack of a positive 6MWT or FEV1 improvement does not necessarily constitute a reason to take the patient off a therapy (ie, discontinue coverage of therapy). For those with insufficient improvement (ie, remaining with markers of high-risk for poor prognosis), rather than discontinuing therapy, escalation in therapy (ie, adding another PAH agent in a different class) may be clinically appropriate for a patient (and is guideline supported) while maintaining a previously initiated agent.[1,2] Moreover, a number of PAH drugs are FDA-approved or guideline-recommended for a variety of clinical goals aside from improvement in 6-minute walk distance or FEV1. Some PAH agents are approved to delay the time to clinical worsening, reduce the risk of disease progression, and/or decrease PAH-related hospitalizations. PAH management has moved to considering multiple parameters to inform severity/mortality risk status. Although 6MWD is a parameter of interest, this is not the only parameter of interest (refer to Table 6). Additionally, FEV1 is not a specified parameter for PAH therapy outcomes in either of the 2 recent guidelines. Notably, treatment goals may be individualized since the lowest-risk profile is not always achievable (per the ESC/ERS guideline).[2]

PA Modification: May consider extending the re-authorization frequency to every 9 or 12 months, consider additional markers for improved disease severity, and consider flexibility for the natural progression of disease. Alternatively, may consider removing this PA criterion because it may prevent providers from being able to continue the initiated drug (in alternative regimens) as the disease progresses, or may contribute to interruptions in therapy and decompensation of the patient's condition.

Overall, the PA form for these agents could be simplified, omitting criteria that have the potential to be misinterpreted by the payer's representative.

Additional Consideration: Patients already on a PAH-drug regimen, prior to securing Medicaid coverage, may be considered for exception (ie, grandfather clause) from having to undergo a new RHC and/or switch to preferred PDL drugs. An attestation field for the provider to express previously initiated regimens (while with another payer) may be incorporated on the PA form to allow continuation of the patient's stable PAH therapy. This may minimize the potential for symptom decompensation and hospitalization due to discontinuation of stabilized therapy.

8.0 SUMMARY

Pulmonary arterial hypertension (PAH) leads to dysfunction of the right ventricle and has a poor prognosis if not promptly treated.[1] Because PAH is a rare and complex, life-threatening disease, ideally patients should be treated at a pulmonary hypertension center of expertise. Rather than focusing on one parameter to determine the patient's prognosis or response to therapy, providers consider many variables to guide treatment decisions. If patients do not respond to escalation of PAH-drug regimens, lung transplantation may be required.

Multi-parameter assessment for determining the patient's severity profile is recommended by recent clinical guidelines.[1,2] This includes assessing WHO FC, exercise capacity, and echocardiographic, laboratory, and hemodynamic variables in order to inform therapeutic decisions (refer to Table 6 for examples of specific parameters). Although treatment goals are individualized, generally speaking, the goal of therapy is to maintain the patient at a low-risk status for poor prognosis.[2]

PAH pharmacotherapy generally includes off-label use of high-dose calcium channel blockers (CCBs) for a subset of PAH cases and administration of agents approved for PAH. The most updated clinical guideline (2022 ESC/ERS) recommends vasoreactivity testing (during right heart catheterization) to determine CCB candidacy for certain subtypes of PAH (IPAH, HPAH, or DPAH); testing patients outside of these subtypes is specifically recommended against.[2] Additionally, CCBs should not be used a) for empiric treatment of PAH (ie, when vasoreactive testing cannot be carried out), b) for PAH that is non-vasoreactive, c) in the presence of right ventricular failure, or d) when there are contraindications to CCBs (refer to Section 5.1).[1] Patients with PAH who are not candidates for vasoreactivity testing or CCBs, or who have an insufficient response to CCB therapy, should be initiated on PAH-specific drug therapy.[2]

While PAH-drug monotherapy is appropriate for some, there are a variety of clinical scenarios for which guidelines recommend combination regimens as initial therapy (eg, dual-therapy with an ERA and PDE5i, or triple-therapy with ERA, PDE5i, and prostacyclin analog), as reviewed in Section 5.0. Moreover, escalation of therapy (ie, add-on therapy) is generally indicated if the initial mono- or dual-therapy is insufficient to meet treatment goals (eg, lower risk status, hemodynamic improvement, etc). Combination regimens comprise agents with different mechanisms of action to induce vasodilation in the pulmonary arterial vasculature and ultimately reduce pulmonary arterial resistance. Selection of therapy depends on patient tolerability and patient-specific treatment goals, as PAH drugs are approved and recommended for a variety of clinical objectives (eg, delay disease progression or clinical worsening, reduce PAH related hospitalization, improve exercise capacity) while also striving to improve the patient's prognosis overall.[1,2]

Section 4.1 reviews the unique indications of the PAH agents. All are approved for the treatment of PAH (ie, WHO PH group 1), and 2 agents (riociguat and treprostinil inhalation) also have non-PAH approved indications. Certain off-label uses for PAH-agents are recommended in the 2022 ESC/ERS pulmonary hypertension guideline, and additional off-label, non-PH uses are indexed in pharmacy compendia (Micromedex and Lexicomp), as summarized in Section 5.2.3.

Points for consideration regarding prior authorization (PA) have been presented in the context of the current PA in place for these agents. Suggested modifications are proposed to encompass FDA-approved

uses (including non-PAH uses) and, potentially, compendia indexed off-label uses. Modifications can be made to accommodate PAH cases that are inappropriate for vasoreactive testing and/or off-label use of high-dose CCB therapy, as such patients with PAH should go on to agents approved for PAH treatment. Certain criteria may be omitted (or specified for treatment-naive patients only), since nuances of disease management may not be accounted for in the criteria with respect to treatment-experienced patients, potentially creating barriers to optimizing and maintaining therapy according to guideline recommended algorithms and patient-specific goals.

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APPENDIX A – CLASSIFICATION OF PULMONARY HYPERTENSION[7,10]

GROUP 1: Pulmonary arterial hypertension (PAH)

- Idiopathic
    - Vasoreactive non-responders
    - Vasoreactive acute responders
- Heritable PAH
- Associated with:
    - Drugs and toxins
    - Connective tissue disease
    - HIV infection
    - Portal hypertension
    - Congenital heart disease
    - Schistosomiasis
- PAH with features of venous/capillary involvement (pulmonary veno-occlusive disease/ pulmonary capillary hemangiomatosis)
- Persistent PH of the newborn

GROUP 2: PH associated with left heart disease

- Heart failure:
    - with preserved ejection fraction
    - with reduced or mildly reduced ejection fraction
- Valvular heart disease
- Congenital/acquired cardiovascular conditions leading to post-capillary PH

GROUP 3: PH associated with lung diseases and/or hypoxia

- Obstructive lung disease or emphysema
- Restrictive lung disease
- Lung disease with mixed restrictive/obstructive pattern
- Hypoventilation syndromes
- Hypoxia without lung disease (high altitude)
- Developmental lung disorders

GROUP 4: PH associated with pulmonary artery obstructions

- Chronic thrombo-embolic pulmonary hypertension (CTEPH)
- Other pulmonary artery obstructions (eg, sarcomas, tumors, arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis)

GROUP 5: PH with unclear and/or multifactorial mechanisms

- Hematological disorders such as chronic hemolytic anemia and chronic myeloproliferative disorders
- Systemic disorders such as sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1.
- Metabolic disorders such as glycogen storage diseases and Gaucher disease
- Chronic renal failure with or without hemodialysis
- Pulmonary tumor thrombotic microangiopathy
- Fibrosing mediastinitis

APPENDIX B – USUAL DOSING FOR PAH DRUGS

Active Ingredient brands	Labeled Adult Dosing[a]
Prostacyclin Analog Vasodilators	
Epoprostenol Flolan 0.5 mg, Veletri 0.5 mg, and generics for reconstitution	**IV infusion**: Start at 2 ng/kg/min; increase to attain therapeutic response, as tolerated[11,25]
Iloprost Ventavis 10 or 20 mcg/mL solution	**Inhalation:** 6-9 inhalations/day of 2.5-5 mcg per inhalation[17]
Treprostinil Tyvaso powder for Inhalation (DPI): 16 to 48 mcg dosage units Tyvaso solution for inhalation: 0.6 mg/mL Remodulin solution for injection: 20 to 200 mg/20 mL; generic available Orenitram ER tablet: 0.125 mg to 5 mg dosage units	**Oral[27]:** Start with 0.25 mg BID or 0.125 mg TID; increase by 0.25 mg BID or 0.125 mg TID every 3-4 days to the highest dose tolerated **Inhalation[18]:** **Solution:** Start at 3 breaths (6 mcg/breath) per treatment session, 4 times per day, 4 hours apart. Gradually up-titrate to 9-12 breaths per session 4 times daily as tolerated and based on response. Each treatment session will take 2-3 minutes. **DPI[24]:** Start with one 16 mcg cartridge per treatment session 4 times daily, separated by 4 hours. Increase dose about every 1-2 weeks by 16 mcg per treatment session to target a maintenance dose of 48-64 mcg per session. **Subcutaneous or IV infusion[26]**: Start at 0.625 to 1.25 ng/kg/min; increase by up to 1.25 ng/kg/min per week per clinical response; after week 4, increase by 2.5 ng/kg/min per week based on clinical response/tolerability
Prostacyclin Receptor Agonist, Vasodilator	
Selexipag Uptravi 1800 mcg for reconstitution for IV use; Uptravi tablets, 200 to 1800 mcg/tablet	**Oral[19]:** Start with 200 mcg BID; increase as tolerated by 200mcg BID at weekly intervals to maximum of 1,600 mcg twice daily **IV[19]**: The IV form is for those temporarily unable to take the oral form. Administer twice daily, as an 80 minute infusion, at the dose that corresponds to the patient's current dose (see package insert table). IV corresponding dosages range from 225 mcg to 1800 mcg BID
Endothelin Receptor Antagonists	
Ambrisentan Letairis 5 mg and 10 mg tablet	**Oral:** Start at 5 mg QD, with or without tadalafil 20 mg QD. At 4-week intervals, increase ambrisentan or tadalafil to 10 mg or 40 mg, respectively, as needed[15]

Active Ingredient brands	Labeled Adult Dosing[a]
Bosentan Tracleer 62.5 mg and 125 mg tablets; generics available Tracleer soluble 32 mg tablet	**Oral:** Initiate at 62.5 mg BID and increase to 125 mg BID after 4 weeks (for those >40kg)[20]
Macitentan Opsumit 10 mg tablet	**Oral:** 10 mg once daily[14]
Phosphodiesterase Type-5 Inhibitors	
Sildenafil Revatio 10mg/12 mL IV solution, generic available Revatio 10 mg/mL oral suspension, generic available Revatio 20mg tablet	**Oral:** 5-20 mg, TID, 4-6 hours apart [21] **Injection**: 2.5-10 mg IV bolus TID [21]
Tadalafil Tadliq 20mg/5 mL or suspension Adcirca 20 mg tablet Alyq 20 mg tablet	**Oral:** 40 mg once daily[16,29]
Soluble Guanylate Cyclase Stimulator	
Riociguat Adempas 0.5 mg to 2.5 mg tablets	**Oral:** 0.5-1.0 mg every 8 hours; increase to maximum dose of 2.5 mg as tolerated[22]

[a] *The usual recommended dose is listed. Refer to prescribing information for dose adjustments in hepatic or renal impairment or special circumstances (eg, drug interactions)*

Abbreviations: BID, twice daily; IV, intravenous; TID, three times daily