COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

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UTAH MEDICAID DUR REPORT
APRIL 2023

TREATMENT FOR PEDIATRIC PULMONARY ARTERIAL HYPERTENSION

Report finalized: March 2023
Report presented: April 2023

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CONTENTS

Contents i

List of Tables iii

Abbreviations iv

1.0 Introduction 1

2.0 Methods 2

3.0 Disease Overview 3

3.1 Classification of Pulmonary Arterial Hypertension (PAH) 3

3.2 Disease Severity 4

4.0 Guideline Recommendations for Diagnosing Pulmonary Hypertension (PH) 5

4.1 Hemodynamic Parameters of PAH 6

4.2 Persistent Pulmonary Hypertension of the Newborn (PPHN) 7

5.0 Treatment Overview 11

5.1 Vasoreactivity Testing to Establish Candidacy for Calcium Channel Blockers (CCBs) 12

5.2 PAH-specific Agents Used for Pediatric Patients 12

5.2.1 Labeled Indications for PAH-specific Agents 13

6.0 Guideline-recommended Treatment for Pediatric PAH 16

6.1 High-dose Calcium Channel Blockers (CCBs) 19

6.2 PAH-specific Agents 19

6.3 Conventional Background Treatment 20

6.4 Assessing Treatment Response 20

6.5 Persistent Pulmonary Hypertension of the Newborn (PPHN) 20

7.0 Other Uses for PAH-specific Agents 26

7.1 Off-label Uses of PAH-specific Agents 26

8.0 Supplemental Pediatric Randomized Controlled Trials 29

8.1 Phosphodiesterase Type 5 Inhibitors 30

8.2 Endothelin Receptor Antagonists 30
8.3 Prostacyclin Analogs 31
9.0 Supplemental Pediatric Observational Studies 31
10.0 Utilization Data 32
11.0 Considerations for Prior Authorization Criteria 33
11.1 Additional Considerations 37
12.0 Summary 38
References 40
Appendix A: Prior Authorization Request Form (June 2022) 48
Appendix B: Literature Search Strategies 50
Ovid Medline – Systematic Reviews 50
Ovid Medline – Randomized Controlled Trials 51
Prostacyclin analogs 51
Ambrisentan 51
Epistemonikos – Systematic Reviews 52
Appendix C: Classification of Pulmonary Hypertension 53
Appendix D: Supplemental Information 55
Mechanism of Action for PAH-specific Agents 55
Pharmacology of PAH-specific Agents 62

LIST OF TABLES

Table 1. Agents Used for the Treatment of PAH in Pediatric Patients 2

Table 2. Clinical Practice Guideline Recommendations for Diagnosing PH in Pediatric Patients 8

Table 3. Risk Stratification for Pharmacotherapy Decision Making in Pediatric PAH 11

Table 4. Labeled Indications of PAH-specific Agents 14

Table 5. Guideline-recommended Pharmacological Agents for Treating Pediatric PAH 17

Table 6. Clinical Practice Guideline Recommendations for the Treatment of Pediatric PAH 22

Table 7. Off-label Indications for PAH-specific Agents 27

Table 8. Evidence for PAH-specific Agents in Pediatric Patients with Pulmonary Hypertension 29

Table 9. 2022 Medicaid FFS Pharmacy Claims Among Pediatric Patients (<18 years of age) 33

Table C1. Classification of Pediatric Pulmonary Hypertension, per ESC/ERS and WSPH 53

Table D1. Mechanism of Action for PAH-specific Agents, Organized by Drug Class 55

Table D2. Labeled Warnings and Precautions for PAH-specific Agents 56

Table D3. Drug-drug Interactions for PAH-specific Agents 60

ABBREVIATIONS

6MWD	6-minute walk distance
AHA	American Heart Association
ATS	American Thoracic Society
AVT	Acute vasodilator testing
BPD	Bronchopulmonary dysplasia
cGMP	Cyclic guanosine monophosphate
CTEPH	Chronic thromboembolic pulmonary hypertension
DRRC	Drug Regimen Review Center
DUR	Drug Utilization Review
ECMO	Extracorporeal membrane oxygenation
EMA	European Medicines Agency
ERA	Endothelin receptor antagonists
ERS	European Respiratory Society
ESC	European Society of Cardiology
FDA	Food and Drug Administration
FFS	Fee-for-service
FEV_1	Forced expiratory volume in 1 second
HPAH	Heritable pulmonary arterial hypertension
iNO	Inhaled nitric oxide
IPAH	Idiopathic pulmonary arterial hypertension
IV	Intravenous
mPAP	Mean pulmonary arterial pressure
PA	Prior authorization
PAH	Pulmonary arterial hypertension
PAH-CHD	Pulmonary arterial hypertension associated with congenital heart disease
PAWP	Pulmonary arterial wedge pressure
PDE5	Phosphodiesterase type 5
PH	Pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
RCTs	Randomized controlled trials
RHC	Right heart catheterization
SC	Subcutaneous
SRs	Systematic reviews
SRMA	Systematic review meta-analysis
TID	Three times daily
US	United States
WHO-FC	World Health Organization functional class
WSPH	World Symposium on Pulmonary Hypertension
WU	Woods units

1.0 INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by increased pulmonary arterial pressure and pulmonary vascular resistance (PVR).[1,2] This disease occurs in infants and children, as well as adults (see note[*]).[3] PAH can arise either idiopathically (ie, with no known cause), or secondary to other contributing conditions (eg, genetic mutation, congenital abnormalities, drug- or toxin-induced, HIV infection).[4] The predominant etiologies in children are idiopathic PAH (IPAH), heritable PAH (HPAH), and PAH due to irreversible congenital heart disease (PAH-CHD).[3,5,6] The majority of PAH cases in the pediatric population occur during infancy (82%); these cases tend to be transient, diagnosed as either repairable cardiac shunt defects or persistent pulmonary hypertension of the newborn (PPHN).[3] If left untreated, PAH progresses into right ventricular heart failure, and eventual death.[7]

Agents approved by the United States (US) Food and Drug Administration (FDA) for the treatment of PAH consist of phosphodiesterase type 5 (PDE5) inhibitors, endothelin receptor antagonists (ERAs), and prostacyclin analogs (**Table 1**). Although the agents listed in **Table 1** may be used for the treatment of PAH in pediatric patients, not all of them are FDA-approved for this age group. Only one agent is specifically approved for use in pediatric patients; bosentan (Tracleer) is approved for use in children ≥3 years of age.[8] Most other agents are labeled more generally without a specified age for use.[9-20] The exception, sildenafil, is approved for adult use only.[21] *According to product labeling*, agents indicated for PAH that do not specify an approved age for use currently lack evidence supporting safety and efficacy in pediatric patients.[9-20] Further, sildenafil is not recommended in children (particularly for long-term use) due to a dose-dependent increase in mortality risk observed in an extension, uncontrolled phase of a lead-in randomized controlled trial (RCT)[22]; however, newer, more robust evidence has shown a decline in mortality risk in pediatric PAH patients treated with sildenafil.[23] Agents approved by the European Medicines Agency (EMA) to treat PAH in pediatric patients include sildenafil, bosentan, and ambrisentan.[3]

The objective of this report is to provide an overview of the pharmacologic treatments for PAH in the pediatric population based on recommendations from the following two guidelines:

- The 2022 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guideline on the diagnosis and treatment of pulmonary hypertension[3]
- The 2015 American Heart Association (AHA) and the American Thoracic Society (ATS) guideline on pediatric pulmonary hypertension[24]

Guidance from the 6th World Symposium on Pulmonary Hypertension (WSPH, 2018) was also included for additional details on the management of pediatric patients with PAH.[5]

[*] For information regarding the management of pulmonary arterial hypertension in adults, please refer to the Drug Utilization Review (DUR) report completed in March 2023, available here: https://medicaid.utah.gov/pharmacy/drug-utilization-review-board/

Table 1. Agents Used for the Treatment of PAH in Pediatric Patients

Drug Class	Active Ingredient	Approved for Pediatric Use for PAH	
		US FDA	EMA[3]
Phosphodiesterase Type 5 Inhibitors	Sildenafil[21]	No; adults only	**Yes; ≥1 year of age**
	Tadalafil[9-11]	Unspecified Age for Use	No; adults only[25]
Endothelin Receptor Antagonists	Bosentan[8]	**Yes; ≥3 years of age**	**Yes; ≥1 year of age**
	Ambrisentan[12]	Unspecified Age for Use	**Yes; ≥8 years of age[26]**
	Macitentan[13]		No; adults only[27]
Prostacyclin Analogs	Epoprostenol[14,15]		Unspecified Age for Use[28]
	Treprostinil[16-19]		No[a]
	Iloprost[20]		No; adults only[29]

[a] *Trepulmix (treprostinil) is available to treat adults with World Health Organization functional class III or IV, and chronic thromboembolic pulmonary hypertension (Group 4 Pulmonary Hypertension)[30]; other formulations are unavailable[31,32]*

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration; PAH, pulmonary arterial hypertension; US, United States

Given the complexity of managing PAH in children and that most of the reviewed agents are not formally FDA-approved for pediatric use, we provide general considerations for prior authorization (PA) criteria, with respect to the most up-to-date PA form (last updated June 2022; see **Appendix A**) as of writing this report.

2.0 METHODS

The focus of this report was to review current guidelines regarding the pharmacotherapeutic management for PAH in pediatric patients. We searched the following websites for guidelines:

- Trip medical database[†]: https://www.tripdatabase.com/
- Lexicomp (referring to the pediatric clinical practice guidelines mentioned within a PAH-specific drug monograph): https://online-lexi-com/
- UpToDate (referring to guidelines listed under the topic of "pulmonary hypertension in children"): https://www.uptodate.com/
- American Thoracic Society: https://www.thoracic.org/statements/pulmonary-vascular.php

We identified two guidelines addressing pharmacotherapy for pediatric PAH: the 2022 ESC/ERS guideline[3] and a 2015 AHA/ATS guideline.[24] To supplement guideline recommendations, we included guidance from international experts in pediatric PAH from the 6th WSHP, convened in 2018.[5]

Product prescribing information (ie, package inserts, product labeling) was obtained from the drug sponsors' website, Drugs@FDA website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm), or the DailyMed website (https://dailymed.nlm.nih.gov/dailymed/).

[†] Search terms: pediatric pulmonary arterial hypertension

To complement the pediatric evidence in the 2022 ESC/ERS guideline for PAH-specific agents, we conducted a literature search for systematic reviews (SRs) of randomized controlled trials (RCTs) in two bibliographic databases: Ovid Medline and Epistemonikos. Supplemental RCT searches were performed when no pediatric RCTs were found in the reviewed SRs for a particular agent, and for RCTs published more recently than the applicable SR. Details of our search strategies, including terms and controlled vocabulary used, are provided in **Appendix B**.

3.0 DISEASE OVERVIEW

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by increased pulmonary arterial pressure and pulmonary vascular resistance (PVR).[1,2] PAH is not only a subset of pulmonary hypertension (PH), but also encompasses several subgroups of various etiologies, including persistent pulmonary hypertension of the newborn (PPHN).[3] The pathophysiology of PAH is due to pulmonary vasculopathy, consisting of vascular remodeling, vasoconstriction, plexiform lesions, medial hypertrophy, and thrombosis formation, fostering vascular narrowing or obstruction of pulmonary arteries.[3]

PPHN is typically characterized as a sustained increase in PVR, with persistent hypoxemia, due to maladaptation of transitioning the fetal pulmonary circulatory system for postnatal life.[24,33] Because PPHN is a syndrome associated with several related disorders (see note[‡]), there tends to be a high risk of mortality, making the need for prompt medical treatment necessary.[24] In a majority of cases, PPHN can be reversed within the first couple days of life if the underlying pulmonary condition is treated.[34] There is the potential for long-term sequelae (eg, hearing deficits, developmental and/or motor delays) in infants with severe PPHN.[35,36]

3.1 Classification of Pulmonary Arterial Hypertension (PAH)

The classification of pulmonary hypertensive conditions is based on shared clinical presentation, hemodynamic parameters, pathophysiology, and therapeutic approach.[3] PAH is one of the five subgroups of PH, referred to as Group 1 PH. Among children, it is the most common type of PH.[3] Another common type among infants and neonates (particularly those that are pre-term) is non-transient PH secondary to developmental lung diseases (eg, bronchopulmonary dysplasia [BPD], congenital pulmonary vascular abnormalities), classified as Group 3 PH.[3,5,6] The clinical classification of PH is identical among pediatric and adult populations, which has been revised over the years by the World Symposium on Pulmonary Hypertension (WSPH) to align with specific pediatric conditions. Refer to **Appendix C** for a complete list of the pulmonary hypertensive conditions, organized by group.

PAH can arise either idiopathically (ie, with no known cause), or secondary to other contributing conditions (eg, genetic mutation, congenital abnormalities, drug- or toxin-induced, HIV infection).[3,4] The

[‡] PPHN can be idiopathic (15% to 20% of cases),[38] but it is described as a syndrome, and therefore, may be associated with the following disorders: down syndrome, meconium aspiration syndrome, myocardial dysfunction, structural cardiac diseases, hepatic and cerebral arteriovenous malformation, respiratory distress syndrome, transient tachypnea of the newborn, pneumonia/sepsis, developmental lung disease, perinatal stress, placental dysfunction (chorioamnionitis, pre-eclampsia, maternal hypertension), metabolic disease, or maternal smoking or drug use[5]

most recent guideline (ESC/ERS)[3] defines the subclassifications of PAH (Group 1 PH) as follows, according to the 6th WSPH (2018)[5]:

- **Idiopathic PAH** (IPAH): includes vasoreactive non-responders and responders
- **Heritable PAH** (HPAH): gene mutations (eg, *TBX4, ACVRL1, BMPR2*)
- **Drug- and toxin-induced PAH**: (eg, diazoxide in neonates)
- **PAH secondary to other conditions**:
    - Connective tissue disease
    - HIV infection
    - Portal hypertension
    - Congenital heart disease
    - Schistosomiasis
- **PAH with overt characteristics of venous/capillary involvement**: pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, or both
- **Persistent pulmonary hypertension of the newborn** (PPHN) syndrome

The predominant etiologies for PAH in children are idiopathic PAH (IPAH), heritable PAH (HPAH), and PAH due to irreversible congenital heart disease (PAH-CHD).[3,5,6] The prevalence of IPAH/HPAH is estimated to be 4.4 per million children, and the prevalence of PAH-CHD is estimated to be 15.6 per million children.[3] The majority of PAH cases in the pediatric population occur during infancy (82%); these cases tend to be transient, diagnosed as either repairable cardiac shunt defects or PPHN.[3] The incidence of PPHN among newborns is higher for those born at earlier gestational ages, with infants born at 22 to 24 weeks having an incidence rate of 18.5%, whereas those born at 27 weeks have a lower incidence rate of 4.4%.[5] Other PAH-related etiologies (eg, PAH secondary to HIV infection, portal hypertension, schistosomiasis) occur less often in children.[3,6]

Before targeted PAH treatments became available, survival from time of diagnosis for children with IPAH was typically 1−2 years, whereas adults tended to survive for 2−3 years after diagnosis.[24] Recently, the prognosis of children with PAH has improved considerably, primarily due to the increased availability of targeted PAH treatments[6]; currently, the predicted five-year survival rate is approximately 60% to 75% for pediatric patients with certain PAH subsets (ie, idiopathic, familial, or secondary to congenital shunting abnormalities).[1]

3.2 Disease Severity

The World Health Organization functional classification (WHO-FC) is one of many parameters used to describe PAH disease severity, and consequently, risk stratification.[3,5,24] Although a functional classification system adapted for pediatric use was suggested in 2011,[37] it has not yet been formally implemented.[5] Therefore, the following definitions are currently used in the general population of patients with PH to assess functional status[3]:

- **WHO-FC I:** Patient has PH, but physical activity is not limited. Conventional physical activity does not result in fatigue, dyspnea, near syncope, or chest pain.

- **WHO-FC II:** Patient has PH, which modestly limits physical activity, but does not cause any discomfort while at rest. Conventional physical activity results in fatigue, dyspnea, near syncope, or chest pain.
- **WHO-FC III:** Patient has PH, which significantly limits physical activity, but does not cause any discomfort while at rest. Less than conventional physical activity results in fatigue, dyspnea, near syncope, or chest pain.
- **WHO-FC IV:** Patient has PH, which causes symptoms at any intensity of physical activity. Dyspnea, fatigue, or both potentially occur at rest, and discomfort is intensified by the degree of physical activity. Signs of right heart failure are present.

Although the WHO-FC is a subjective evaluation, it is a strong predictor of survival in pediatric patients and can be used for setting treatment goals.[5] Notably, it may be particularly challenging to assign young children a WHO-FC due to the absence of exercise standards in children under 8 years of age, and the limited number of RCTs available for therapy guidance.[24]

The 2022 ESC/ERS and 2015 AHA/ATS guidelines use risk stratification to describe PAH disease severity and to determine the initial pharmacotherapeutic approach (see **Section 5.0**) in children with PAH.[3,24] Risk stratification into low or high risk categories is determined by assessing multiple parameters including WHO-FC, 6-minute walk distance (6MWD) test in patients 6 years of age and older, brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) biomarkers, symptom progression, signs of right ventricular failure, and a variety of laboratory assessments (eg, arterial hemodynamics, echocardiography, cardiopulmonary exercise testing).[3,5,24]

4.0 GUIDELINE RECOMMENDATIONS FOR DIAGNOSING PULMONARY HYPERTENSION (PH)

Due to the diverse etiologies of PH, a comprehensive diagnostic work-up (tailored to age) is recommended by guidelines to ensure a correct diagnosis and treatment strategy are implemented.[3,5] Because the disease state is complex and clinical expertise is required for performing the diagnostic procedures (ie, heart catheterization), it is recommended that pediatric care of PH occur in specialized PH centers by a multidisciplinary team (eg, pulmonologists, cardiologists).[3,24] It is important to consider age-appropriateness of tests (eg, 6-minute walk distance [6MWD])[24] because infants and young children may be unable to perform or tolerate certain tests.[6] Ideally, the 6MWD test should be used in children at least 6 years of age.[5]

The following assessments and laboratory tests are recommended to be performed by the 2015 AHA/ATS guideline and clinical experts from the 6th WSPH[5,24]:

Assessments upon suspicion of PH in pediatric patients – step 1:

- Echocardiogram (*preferred noninvasive test*), electrocardiogram, chest x-ray

Assessments upon suspicion of PH due to an associated lung disease – step 2:

- Pulmonary function tests, including diffusing capacity of the lung for carbon monoxide
- Polysomnography
- Chest computed tomography, with and without contrast

Assessments upon suspicion of chronic thromboembolic pulmonary hypertension (CTEPH) – step 3:

- Ventilation/perfusion scan

Assessment for diagnosing PH – step 4:

- Cardiac catheterization with acute vasodilator testing (AVT)

The 2015 AHA/ATS guideline also recommended measuring biomarkers (BNP or NT-proBNP) at the time of diagnosis and at follow-up visits to aid clinical decision making.[24] These biomarkers can be used to monitor treatment response because they tend to be elevated with right- or left- ventricle failure, or atrial dilatation. As appropriate, additional imaging (eg, cardiac magnetic resonance imaging) is recommended to diagnose other related conditions (eg, pulmonary artery stenosis, parenchymal lung disease, pulmonary thromboembolic disease) upon the suspicion of PH, or to evaluate changes in cardiac chamber dimensions and ventricular functioning at follow-up visits. The 2015 AHA/ATS guideline recommended serial echocardiograms after completing the initial evaluation, with echocardiograms performed more often if alterations in the patient's clinical condition or treatment occurs.[24]

Because pediatric PAH can be associated with genetic disorders, and syndromic and chromosomal anomalies, the 2022 ESC/ERS guideline commented that genetic testing can be considered among pediatric patients[3]; whereas the 2015 AHA/ATS guideline suggested genetic testing for select patients, such as those with a family history of PAH or IPAH.[24] Genetic testing can be considered to stratify risk, determine the causative PH etiology, and identify at risk family members, which is especially important for first-degree relatives of pediatric patients with monogenic forms of HPAH,[24] but should be performed after appropriate individual and family genetic counseling.[3,24]

With the exception of PPHN diagnosis (a subgroup of PAH), the gold standard for diagnosing PH in children is right heart catheterization (RHC) to measure arterial hemodynamic parameters.[3,24] RHC is recommended to be performed before PAH-specific treatment is initiated[3,24]; however, exceptions may exist such as critically ill patients who need to start empirical treatment immediately (eg, WHO-FC IV).[24] In children with PH, cardiac catheterization can cause serious complications, especially for patients who are in a worse clinical state or are young infants.[3] Therefore, it is recommended to perform cardiac catheterization after weighing the individualized benefits and risks, and within a specialized PH center, preferably one that is experienced in pediatric management.[3]

4.1 Hemodynamic Parameters of PAH

The general definition of PH in pediatric patients (>3 months of age) is identical to adults, requiring a resting mean pulmonary arterial pressure (mPAP) of >20 mmHg.[3] The older 2015 AHA/ATS guideline has the historical definition of mPAP ≥25 mmHg.[24] To identify pre-capillary PH (which is characteristic of PAH and some other types of PH) additional criteria of a pulmonary vascular resistance index (PVRI) of ≥3 Woods units (WU)•m^2, and a pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg should be confirmed using heart catheterization at a specialized PH center,[3,24] preferably a center experienced in pediatric managemanet.[3]

4.2 Persistent Pulmonary Hypertension of the Newborn (PPHN)

PPHN (a subclassification of PAH) has distinct diagnostic recommendations. Initial evaluation of PPHN consists of a physical examination, pre- and post-ductal oxygen saturation, arterial blood gas testing, and chest radiography, but the gold standard for diagnosing PPHN is echocardiography.[3,33,38] Furthermore, RHC may have limited utility, or may even be contraindicated,[39] in infants with suspected PPHN.[3] Suggestive echocardiography findings of PPHN include signs of PH, such as flattening of the interventricular septum and right ventricle hypertrophy or dilatation.[33] Echocardiography can also identify areas of extrapulmonary shunting, and the presence or absence of ventricular dysfunction.[38]

PPHN is not defined by certain hemodynamic thresholds,[40] but rather clinical presentation (eg, hypoxemia) and echocardiography findings. For example, if right-to-left shunting exists and no congenital abnormalities are present, the diagnosis of PPHN is confirmed, irrespective of the pulmonary arterial pressure.[40]

Table 2 summarizes guideline recommendations for the general diagnosis of PH in pediatric patients, including infants.

Table 2. Clinical Practice Guideline Recommendations for Diagnosing PH in Pediatric Patients

2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension[3]	Recommendation Class, LoE
Children	
• Similar to adults with pulmonary hypertension, a comprehensive work-up should be performed in children with pulmonary hypertension to confirm the diagnosis and causative etiology, but the approach should be modified for age	**Class I, Level C**
• Right heart catheterization and acute vasodilator testing, along with other diagnostic evaluations, and treatment should be performed at specialized pulmonary hypertension centers, preferably at those experienced in pediatric management	**Class I, Level C**
○ Ideally before starting any PAH agents, right heart catheterization is recommended to confirm the diagnosis of pulmonary hypertension	**Class I, Level C**
• It is recommended to use acute vasoreactivity testing in pediatrics with IPAH/HPAH to identify whether CCBs may be beneficial	**Class I, Level C**
• A positive response to acute vasoreactivity testing is the same in adults and children: a decrease in mean PAP ≥10 mmHg to achieve an overall value of mean PAP ≤40 mmHg, with an unaffected or increased cardiac output	**Class I, Level C**
Infants	
• Infants presenting with bronchopulmonary dysplasia are recommended to be screened for pulmonary hypertension	**Class I, Level B**
• For infants with pulmonary hypertension and/or at risk for bronchopulmonary dysplasia, it is recommended to optimize respiratory support and treat any underlying lung conditions, including aspiration, hypoxia, and structural airway disease, before starting PAH agents	**Class I, Level B**
• Given that pulmonary hypertension in neonates and infants is often due to developmental lung disease (ie, vascular or parenchymal), a customized diagnostic and therapeutic approach, different from older children and adults, can be considered	**Class IIa, Level C**
2015 AHA/ATS Guideline on Pediatric Pulmonary Hypertension[24]	**Recommendation Class, LoE**
General assessments	

2022 ESC/ERS and 2015 AHA/ATS Guidelines: ***Recommendation Class****: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention should be considered; Class IIb, the intervention may be considered; Class III, the intervention is not recommended.* ***Level of Evidence****: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on large non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, and/or retrospective studies, case studies, small studies, registries, standard of care.*

Abbreviations: 6MWD, 6-minute walk distance, AHA, American Heart Association; ATS, American Thoracic Society; BNP, brain natriuretic peptide; CCBs, calcium channel blockers; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; LoE, level of evidence; MRI, magnetic resonance imaging, NT-proBNP, N-terminal pro-brain natriuretic peptide, PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure, PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance

Table 2. Clinical Practice Guideline Recommendations for Diagnosing PH in Pediatric Patients

• Before starting treatment, the following should be completed at a specialized center upon initial diagnosis of pulmonary hypertension: a) a comprehensive examination including physical assessment and history, b) diagnostic testing to determine the etiology and classification of the pulmonary hypertension, and c) cardiac function assessment	**Class I, Level B**
• At the time of diagnosis, appropriate imaging should be performed if the following conditions are suspected: a) pulmonary thromboembolic disease, b) pulmonary vein stenosis, c) peripheral pulmonary artery stenosis, d) parenchymal lung disease, or e) PVOD	**Class I, Level B**
• To provide additional clinical insights, BNP or NT-proBNP is recommended to be measured at the time of diagnosis and follow-up visits	**Class I, Level B**
• To evaluate changes in cardiac chamber dimensions and ventricular functioning, MRI can be considered at follow-up visits or included in the diagnostic assessment	**Class IIa, Level B**
• Pediatric patients with pulmonary hypertension who are of an appropriate age should have 6MWD test to evaluate exercise tolerance	**Class I, Level A**
• A sleep study is recommended to be included in the diagnostic assessment for pediatric patients with pulmonary hypertension who are at risk of sleep-disordered breathing, or as part of an assessment for those who inadequately respond to PAH-specific agents	**Class I, Level B**
• Serial echocardiograms are recommended after completing the initial evaluation. If alterations in the patient's clinical condition or treatment occurs, echocardiograms are recommended to be performed more often	**Class I, Level B**
Cardiac catheterization	
• Before starting PAH-specific agents, it is recommended to perform cardiac catheterization. However, exceptions may exist such as critically ill patients who need to start empirical treatment immediately	**Class I, Level B**
• Unless a contraindication exists, acute vasoreactivity testing should be included as part of the cardiac catheterization	**Class I, Level A**
• A positive response to acute vasoreactivity testing is at minimum a ≥20% reduction in PAP and PVR/SVR, with no reduction in cardiac output	**Class I, Level B**

*2022 ESC/ERS and 2015 AHA/ATS Guidelines: **Recommendation Class**: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention should be considered; Class IIb, the intervention may be considered; Class III, the intervention is not recommended. **Level of Evidence**: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on large non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, and/or retrospective studies, case studies, small studies, registries, standard of care.*

Abbreviations: 6MWD, 6-minute walk distance, AHA, American Heart Association; ATS, American Thoracic Society; BNP, brain natriuretic peptide; CCBs, calcium channel blockers; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; LoE, level of evidence; MRI, magnetic resonance imaging, NT-proBNP, N-terminal pro-brain natriuretic peptide, PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure, PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance

Table 2. Clinical Practice Guideline Recommendations for Diagnosing PH in Pediatric Patients

• After starting treatment, it is recommended to repeat cardiac catheterization within 3 to 12 months to determine treatment response, or with clinical deterioration	**Class I, Level B**
○ Indicators for repeat catheterizations with acute vasoreactivity testing include clinical deterioration or lack of improvement with treatment, but ultimately, the timing should be based on the provider's judgement	**Class I, Level B**
• Serial cardiac catheterizations with acute vasoreactivity testing should be performed at follow-up to evaluate prognosis and potential modifications in treatment	**Class I, Level B**
Genetic testing	
• Genetic testing and counseling can be considered for children with IPAH or HPAH	**Class IIa, Level C**
• First-degree relatives of pediatric patients with monogenic forms of HPAH can be considered for genetic testing:	
○ For the purposes of risk stratification	**Class I, Level B**
○ Screen for asymptomatic carriers using noninvasive procedures (eg, echocardiograms)	**Class IIa, Level B**
• Family members of patients with HPAH should be immediately evaluated for PAH if new cardiopulmonary symptoms arise	**Class I, Level B**
• Family members of pediatric patients with pulmonary hypertension associated with genetic syndromes should be educated on the related symptoms and the need to seek prompt medical care if symptoms occur in the affected child	**Class I, Level B**
Infants	
• Infants with bronchopulmonary dysplasia should be screened for pulmonary hypertension with echocardiogram	**Class I, Level B**
• For infants with pulmonary hypertension and bronchopulmonary dysplasia, it is recommended to optimize respiratory support and treat any underlying lung conditions, including aspiration, hypoxemia, and structural airway disease, before starting PAH-specific agents	**Class I, Level B**

2022 ESC/ERS and 2015 AHA/ATS Guidelines: ***Recommendation Class****: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention should be considered; Class IIb, the intervention may be considered; Class III, the intervention is not recommended.* ***Level of Evidence****: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on large non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, and/or retrospective studies, case studies, small studies, registries, standard of care.*

Abbreviations: 6MWD, 6-minute walk distance, AHA, American Heart Association; ATS, American Thoracic Society; BNP, brain natriuretic peptide; CCBs, calcium channel blockers; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; LoE, level of evidence; MRI, magnetic resonance imaging, NT-proBNP, N-terminal pro-brain natriuretic peptide, PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure, PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance

5.0 TREATMENT OVERVIEW

Treating PAH in children relies on disease-severity-based risk stratification.[3,5,24] Generally, prognostic determinants in pediatric patients are similar to those of adults and include signs of right ventricular failure, progression of symptoms, WHO-FC, 6MWD test (if applicable to age), biomarker levels, echocardiography findings, and hemodynamic parameters.[3] Although it is currently unclear how many lower- or higher-risk criteria are required to guide therapeutic decisions, a higher number of either should be considered as a valid reason for initiating treatment.[5]

Table 3 highlights the parameters that are attributed to PAH disease severity and prognosis.

Table 3. Risk Stratification for Pharmacotherapy Decision Making in Pediatric PAH[3,5,24]

Determinants of Prognosis[3]	Lower Risk for Poor Prognosis	Higher Risk for Poor Prognosis
Signs of right ventricular failure[5,24]	None	Present
Progression of symptoms[5]	None	Present
WHO-FC[5,24]	I ,II	III, IV
6MWT (aged >6 years)[5,24]	2019 WSPH: >350 m 2015 AHA/ATS: >500 m	2019 WSPH: <350 m 2015 AHA/ATS: <300 m
Biomarkers BNP or NT-proBNP[5,24]	Modestly elevated	Drastically elevated
Echocardiography[5,24]	Minimal right ventricular dysfunction or enlargement	• Significant right atrium or ventricular enlargement or dysfunction (eg, low TAPSE, increased ratio of right-to-left ventricles) • Decreased left ventricular size • Pericardial effusion
Hemodynamics[5,24]	• CI >3.0 L/min/m^2 • Systemic venous saturation >65% • PVRI <10 WU• m^2 • PVR/SVR <0.5 • Acute vasoreactivity	• CI <2.5 or 2.0 L/min/m^2 • Systemic venous saturation <60% • PVRI >20 WU• m^2 • PVR/SVR >1.0 • PACI <0.85 mL/mmHg/m^2
Syncope[24]	None	Recurrent episodes
Growth[5]	As expected	Failure to thrive
CPET[24]	Peak VO_2 >25 mL/kg/min	Peak VO_2 <15 mL/kg/min

Abbreviations: 6MWT, 6-minute walk test; AHA, American Heart Association; ATS, American Thoracic Society; BNP, brain natriuretic peptide; CI, cardiac index; CPET, cardiopulmonary exercise testing; ERS, European Respiratory Society; ESC, European Society of Cardiology; NT-proBNP, N-terminal pro-brain natriuretic peptide; PACI, pulmonary arterial compliance index; PAH, pulmonary arterial hypertension; PVR(I), pulmonary vascular resistance (index); SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization functional class; WU, Wood Units

5.1 Vasoreactivity Testing to Establish Candidacy for Calcium Channel Blockers (CCBs)

Acute vasoreactivity testing (AVT) with a vasodilator (eg, inhaled nitric oxide, inhaled iloprost intravenous epoprostenol)[3,5,24] is used to identify whether high-dose calcium channel blockers (CCBs) may be beneficial.[3,24] The 2015 AHA/ATS guideline recommended AVT with cardiac catheterization, unless a contraindication exists,[24] whereas the 2022 ESC/ERS guideline recommended AVT for select pediatric patients: those with IPAH or HPAH.[3] In the 2022 ESC/ERS guideline, the same criteria for a positive response is used in adults and children,[3] but the 2015 AHA/ATS guideline uses a definition that has been adapted for the pediatric population.[24] The following criteria indicate a positive response to AVT in pediatric patients:

- **2022 ESC/ERS guideline[3]**: A decrease in mPAP ≥10 mmHg to achieve an overall value of mPAP ≤40 mmHg, with an unaffected or increased cardiac output
- **2015 AHA/ATS guideline[24]**: At minimum, a ≥20% reduction in pulmonary artery pressure and pulmonary vascular resistance (PVR)/systemic vascular resistance, with no reduction in cardiac output

5.2 PAH-specific Agents Used for Pediatric Patients

The goal of treatment is to improve longevity and foster participation in childhood activities, without being burdened by disease limitations.[3,5] Current pharmacotherapies are not curative.[7,39] Guideline-recommended treatment for pediatric PAH includes conventional heart failure treatment (eg, diuretics, oxygen, digoxin), the use of high-dose CCBs (eg, diltiazem, amlodipine) for positive responders to AVT, and PAH-specific agents from three drug classes: prostacyclin analogs, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors.[3,24] Prostacyclin analogs, ERAs, and PDE5 inhibitors target differing pathophysiologic pathways of PAH to modulate vasoconstriction in the pulmonary arteries. Refer to **Appendix D** for information on the pharmacology and mechanism of action (**Table D1**), labeled warnings and precautions (**Table D2**), and clinically relevant drug interactions (**Table D3**) for PAH-specific agents.

In this report, drugs that are FDA-approved for PAH are referred to as “PAH-specific” pharmacotherapies.

5.2.1 Labeled Indications for PAH-specific Agents

The only agent specifically FDA-approved for use in pediatric patients (≥3 years of age) is bosentan (Tracleer).[8] Except for sildenafil (FDA-approved for adults only),[21] the remaining agents are labeled more generally without a specified age for use.[9-20] *According to product labeling*, agents indicated for PAH that do not specify an approved age for use currently lack evidence supporting safety and efficacy in pediatric patients.[9-20]

Although each of the PAH-specific agents are approved for the management of PAH, the indicated purpose for use in PAH (highlighted in *blue text* below) varies by agent and, in some instances, by formulation[8-21]:

- *Delay disease progression*: oral treprostinil
- *Reduce risk of disease progression*: macitentan, ambrisentan with tadalafil
- *Delay clinical worsening*: ambrisentan, sildenafil
- *Reduce clinical worsening*: bosentan in adult patients
- *Improve exercise capacity or ability*: ambrisentan with tadalafil, oral and inhaled treprostinil, tadalafil, sildenafil, epoprostenol, bosentan
- *Minimize exercise-related symptoms*: injectable treprostinil
- *Reduce the risk of PAH-related hospitalization*: ambrisentan with tadalafil, macitentan
- *Reduce the rate of clinical worsening in patients who switch from epoprostenol*: injectable treprostinil
- *Improve the composite outcome of symptoms, clinical deterioration, and exercise tolerance*: iloprost
- *Improve pulmonary vascular resistance*: bosentan in pediatric patients

Table 4 summarizes the labeled indication for each formulation. Notably, the inhaled formulations of treprostinil are also FDA-approved for improving exercise ability in patients with PH secondary to interstitial lung disease (Group 3 PH).[18,19]

Note: despite the labeled indications for PAH-specific agents, there is some evidence to support the use of certain agents for the treatment of PAH in pediatric patients, as reviewed in the next section.

Table 4. Labeled Indications of PAH-specific Agents

Active Ingredient Brand Name	Labeled Indication
Prostacyclin Analogs	
Epoprostenol[14,15] Veletri: 0.5 mg or 1.5 mg for reconstitution Flolan: 0.5 mg or 1.5 mg for reconstitution	*IV infusion:* approved for treating patients with PAH to improve exercise capacity
Iloprost[20] Ventavis: 10 mcg/mL or 20 mcg/mL solution for oral inhalation	*Oral inhalation:* approved for treating patients with PAH to improve the composite outcome of symptoms (NYHA Class), clinical deterioration, and exercise tolerance
Treprostinil[16-19]	
Remodulin: 20 mg, 50 mg, 100 mg, 200 mg, or 400 mg solution for injection, supplied as 20 mL vials	*IV or SC injection:* approved for a) treating patients with PAH to minimize exercise-related symptoms, b) reduce the rate of clinical worsening in patients who switch from epoprostenol
Tyvaso: 0.6 mg/mL solution for oral inhalation Tyvaso DPI: 16 mcg, 32 mcg, 48 mcg, or 64 mcg dry powder, for oral inhalation	*Oral inhalation:* approved for a) treating patients with PAH to improve exercise ability, b) improve exercise ability in patients with PH secondary to interstitial lung disease (Group 3 PH)
Orenitram: 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, or 5 mg ER tablets, for oral use	*Oral tablets:* approved for treating patients with PAH to improve exercise capacity and delay disease progression
Endothelin Receptor Antagonists	
Ambrisentan[12] Letairis: 5 mg or 10 mg tablets for oral use	*Oral tablets:* approved for treating patients with PAH to a) delay clinical worsening and improve exercise ability, b) when used concomitantly with tadalafil, reduce the risk of PAH-related hospitalization and disease progression, and improve exercise ability
Bosentan[8] Tracleer: 62.5 mg or 125 mg film-coated tablets for oral use Tracleer: 32 mg soluble tablet for oral suspension	*Oral tablets:* approved for treating a) **adults** with PAH to reduce clinical worsening and improve exercise ability, b) **pediatric patients** (≥3 years of age) with congenital PAH or IPAH to improve PVR, and potentially exercise ability
Macitentan[13] Opsumit: 10 mg tablets for oral use	*Oral tablets:* approved for treating patients with PAH to reduce the risk of PAH-related hospitalization and disease progression

Abbreviations: DPI, dry powder inhaler; ER, extended-release; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SC, subcutaneous

Table 4. Labeled Indications of PAH-specific Agents

Active Ingredient Brand Name	Labeled Indication
Phosphodiesterase Type 5 Inhibitors	
Sildenafil[21] Revatio: 20 mg tablets, for oral use Revatio: 10 mg/12.5 mL solution for injection Revatio: 10 mg/mL suspension for oral use	*Oral tablets or inhalation, or IV injection:* approved for treating **adults** with PAH to delay clinical worsening and improve exercise ability
Tadalafil[9-11] Alyq: 20 mg tablets for oral use Adcirca: 20 mg tablets for oral use Tadliq: 20 mg/5 mL suspension for oral use	*Oral tablets or suspension:* approved for treating patients with PAH to improve exercise ability

Abbreviations: DPI, dry powder inhaler; ER, extended-release; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; SC, subcutaneous

6.0 GUIDELINE-RECOMMENDED TREATMENT FOR PEDIATRIC PAH

Unfortunately, the evidence for the management of PAH among pediatric patients is limited, with most RCTs including only adults.[24] Therefore, treatment algorithms are necessarily extrapolated from adults and supplemented by evidence from observational studies of children with PAH.[3]

The 2022 ESC/ERS guideline provides a summary of the level of evidence (available at the time of their review) for the use of PAH-specific agents in the pediatric population, ranging from randomized controlled trials (RCTs) to cohort studies.[3] Although older, the 2015 AHA/ATS guideline denotes a recommendation class for each agent based on the level of evidence available at that time.[24] **Table 5** provides the guideline-recommended dosing and level of evidence for the use of prostacyclin analogs (ie, **epoprostenol, treprostinil**), PDE5 inhibitors (ie, **sildenafil, tadalafil**), and ERAs (ie, **bosentan, ambrisentan, macitentan**) in the pediatric population. Notably, newer agents used in the management of adult PAH, including selexipag and riociguat, had insufficient evidence in pediatric patients at the time of the ESC/ERS guideline's evidence review.[3] Refer to **Section 8.0** for additional details about the available RCT evidence for PAH-specific agents in the pediatric population.

The 2022 ESC/ERS guideline provides treatment recommendations with respect to age groups (children, infants), but does not define age thresholds.[3] The 2015 AHA/ATS guideline delineates recommendations based on the specific PH classifications (eg, idiopathic PAH, PPHN),[24] which in some instances, can be an indicator of age.

Initial treatment depends on a) presence of cardiovascular-related complications (eg, hypoxia, reduced cardiac output), b) vasoreactivity response, and c) risk stratification for poor prognosis (see **Table 3**).

Table 5. Guideline-recommended Pharmacological Agents for Treating Pediatric PAH

Active Ingredient Formulation	Guideline-recommended Dosing[3,24]	Study Design for Pediatric Patients, Per 2022 ESC/ERS[3]	Recommendation Class, LOE, Per 2015 AHA/ATS[24]
Prostacyclin Analogs			
Epoprostenol Intravenous infusion	• Initial dose: 1 to 2 ng/kg/min, with no known maximum • Stable dose: typically 40 to 80 ng/kg/min • It may be necessary to increase the dose	Retrospective cohort studies	**Class I, Level B**
Iloprost Inhalation	Dosing not yet determined in pediatric patients	• Insufficient evidence • Small, retrospective case series	**Class IIa, Level B**
Treprostinil Intravenous Subcutaneous	• Initial dose: 2 ng/kg/min, with no known maximum • Stable dose: typically 50 to 100 ng/kg/min • It may be necessary to increase the dose	Retrospective cohort studies	**Class I, Level B**
Inhalation	• 1 to 9 inhalations (patient-activated) every 6 hours	--	**Class IIa, Level B**
Oral	• Dosing not yet determined in pediatric patients	--	--
Endothelin Receptor Antagonists			
Ambrisentan Oral	Recommended dosing: 2.5 mg to 10 mg per day, as a single dose	Uncontrolled, open-label trial	**Class IIa, Level B**

Bosentan
Oral
	• Starting dose is taken for the first 4 weeks of treatment, followed by the maintenance dose
	  ○ The starting and maintenance dose is the same in patients ≤12 years of age, and patients >12 years of age who weigh <40 kg
	• Dosage based on weight (per product labeling)[8]
	  ○ Patients >12 years of age:
	  ▪ <40 kg: 62.5 mg BID
	  ▪ >40 kg: Starting dose: 62.5 mg BID; Maintenance dose: 125 mg BID
		Uncontrolled, open-label studies	**Class I, Level B**

*2015 AHA/ATS Guideline: **Recommendation Class**: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention is reasonable; Class IIb, the intervention may be considered; Class III, the intervention is not recommended. **Level of Evidence**: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, case studies, or standard of care*

Abbreviations: AHA, American Heart Association; ATS, American Thoracic Society; BID, twice daily; EMA, European Medicines Agency; ERS, European Respiratory Society; ESC, European Society of Cardiology; FDA, Food and Drug Administration; IPAH, idiopathic pulmonary arterial hypertension; LoE, level of evidence; PAH, pulmonary arterial hypertension; TID, three times per day

Table 5. Guideline-recommended Pharmacological Agents for Treating Pediatric PAH

Active Ingredient Formulation	Guideline-recommended Dosing[3,24]	Study Design for Pediatric Patients, Per 2022 ESC/ERS[3]	Recommendation Class, LOE, Per 2015 AHA/ATS[24]
	○ Patients ≤12 years of age: ▪ ≥4 to 8 kg: 16 mg BID ▪ >8 to 16 kg: 32 mg BID ▪ >16 to 24 kg: 48 mg BID ▪ >24 to 40 kg: 64 mg BID		
Macitentan Oral	Dosing not yet determined in pediatric patients	• Insufficient evidence • Ongoing, open-label study	--
Phosphodiesterase Type 5 Inhibitors			
Sildenafil Oral	• Age <1 year: 0.5 to 1 mg/kg TID • Weight <20 kg: Daily total dose of 30 mg, taken as 10 mg in 3 doses • Weight ≥20 kg: Daily total dose of 60 mg, taken as 20 mg in 3 doses • Avoid higher doses (>3 mg/kg/day) in pediatric patients due to the increased risk of mortality	Randomized, open-label, controlled trial	**Class I, Level B**
Tadalafil Oral	• Initial dose: 0.5 to 1 mg/kg/day, as a single dose • Maximum dose: 40 mg daily • Dosing was only studied in children >3 years of age	Randomized, open-label, controlled trial	**Class IIa, Level B**

*2015 AHA/ATS Guideline: **Recommendation Class**: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention is reasonable; Class IIb, the intervention may be considered; Class III, the intervention is not recommended. **Level of Evidence**: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, case studies, or standard of care*

Abbreviations: AHA, American Heart Association; ATS, American Thoracic Society; BID, twice daily; EMA, European Medicines Agency; ERS, European Respiratory Society; ESC, European Society of Cardiology; FDA, Food and Drug Administration; IPAH, idiopathic pulmonary arterial hypertension; LoE, level of evidence; PAH, pulmonary arterial hypertension; TID, three times per day

6.1 High-dose Calcium Channel Blockers (CCBs)

In the absence of contraindications to calcium channel blockers (CCBs), high-dose, oral CCBs are recommended for children who have a positive response to AVT,[5,24] and who are at least 1 year of age (according to the 2015 AHA/ATS guideline).[24] The 2022 ESC/ERS guideline recommended AVT, and thus CCB use, only for pediatric patients with a specific subtype of PAH: IPAH or HPAH.[3] Treatment with CCBs can be continued in pediatric patients who maintain clinical improvement, but add-on treatment with PAH-specific agents may be needed in patients who experience clinical worsening.[5] Treatment with CCBs requires frequent follow-up due to the potential for long-term CCB treatment to fail.[3] According to the 2015 AHA/ATS guideline, recommended CCBs include diltiazem, nifedipine, and amlodipine.[24] CCBs are contraindicated in patients who have not had, or did not respond to AVT, and in patients who suffer from right-sided heart failure.[24] Additionally, CCBs may be considered inappropriate based on the provider's clinical judgement in the following scenarios:

- The patient has a PAH subtype where evidence for CCB therapy is lacking[3]
- The risks of performing AVT, and thus using CCBs are determined to be too high
    - Patients who are more likely to experience unfavorable outcomes during AVT are those with WHO-FC IV symptoms, low cardiac output, low systemic blood pressure, or pulmonary veno-occlusive disease.[41]

6.2 PAH-specific Agents

Risk stratification is used to guide therapeutic treatment decisions for pediatric patients who are inappropriate for AVT/CCBs or who showed an inadequate or non-sustained response to CCBs.[3,5,24]

Oral monotherapy with either an ERA (bosentan or ambrisentan) or PDE5 inhibitor (tadalafil or sildenafil) is recommended as *initial* treatment for lower-risk pediatric patients.[5,24] Early combination treatment with an inhaled prostacyclin analog (treprostinil or iloprost) may also be beneficial for lower-risk patients, especially those who experience clinical worsening.[5] As a goal-oriented approach, PAH-specific agents can be added in a manner to achieve individualized clinical goals or therapeutic values.[24] Relative to monotherapy, combination treatment with PAH-specific agents from differing drug classes may provide an additive, sustained effect by targeting multiple pathophysiologic pathways involved in PAH.[24]

Higher-risk pediatric patients should be immediately initiated on a subcutaneous (SC) or intravenous (IV) prostacyclin analog (treprostinil or epoprostenol).[5,24] Early combination treatment can also be considered for higher-risk patients; based on a 2019 European consensus statement, early combination treatment with an IV or SC prostacyclin agonist, in addition to an oral PDE5 inhibitor and ERA can be considered.[39] Regarding transitioning from parenteral to inhaled or oral preparations, the 2015 AHA/ATS guideline recommended considering transitioning when patients improve to an asymptomatic status with continual, near-normal pulmonary hemodynamic parameters.[24] Importantly, transitioning from parenteral to inhaled or oral dosage formulations should be performed in specialized pediatric PH centers.[24] Higher-risk pediatric patients who experience clinical worsening despite optimal medical intervention[5] and recommended pharmacotherapies, or who are unable to access PAH-specific agents, should be considered for lung transplant and interventional palliative surgical procedures (eg, atrial

septostomy, Potts shunt; which act as interims to lung transplantation while waiting for an organ donor).[3,5]

6.3 Conventional Background Treatment

Conventional heart failure treatments (eg, digoxin, diuretics, warfarin, oxygen) can be considered, but should be implemented based on patient-specific factors.[5] For example, digoxin and diuretics are recommended to be used if signs of right-sided heart failure exist, but should be initiated cautiously to ensure intravascular volume is not excessively reduced.[5,24] Additionally, anticoagulation with warfarin on a chronic basis can be considered for pediatric patients with IPAH or HPAH, as well as other conditions (eg, reduced cardiac output, predisposition to hypercoagulable disorders, chronic indwelling catheter); however, anticoagulation should be avoided in young children with PAH due to the potential risk of hemorrhagic complications.[24] Supplemental oxygen can be considered for pediatric patients with PAH if their oxygen saturation is below 92%; this may be particularly beneficial for patients with PAH due to an underlying respiratory condition.[24]

6.4 Assessing Treatment Response

For patients with PAH, a crucial aspect of disease management is monitoring treatment response and disease progression.[3] The 2022 ESC/ERS guideline recommended that an age-appropriate treatment plan be based on the child's PAH risk category and treatment response. Generally, acquiring a low-risk category of PAH and sustaining the lower-risk profile is considered an indicator of a positive treatment response. Although this is the ideal response, individualized treatment goals should be made because achieving a low-risk profile is not always feasible. Several factors contribute to mortality risk in PAH, including WHO-FC, serum biomarkers (NT-proBNP), and tricuspid annular plane systolic excursion (TAPSE), which could be used as potential markers for treatment response.[3]

The 2015 AHA/ATS guideline recommended repeat cardiac catheterizations within 3 to 12 months after starting treatment to determine treatment response, or with clinical deterioration.[24] However, the newer ESC/ERS guideline describes that "…indications for repeated RHC in children with PH are currently not well defined."[3] (page 79) Ultimately, response to treatment should be based on a culmination of information obtained from echocardiographic findings, biomarker levels, clinical evaluation, and exercise tests.[3]

6.5 Persistent Pulmonary Hypertension of the Newborn (PPHN)

Although proposed treatment algorithms for infants with persistent pulmonary hypertension of the newborn (PPHN) were considered outside the scope of the 2022 ESC/ERS guideline, and specific recommendations for this condition were not provided, this guideline commented that neonates and infants often have PH due to developmental lung diseases (ie, vascular or parenchymal); therefore, a customized diagnostic and therapeutic approach, different from older children and adults, can be considered in this population.[3] PPHN can arise secondary to lung parenchymal diseases (eg, respiratory distress syndrome, pneumonia), resulting in abnormal vasoconstriction of the pulmonary vasculature.[33]

The vasodilator of choice for treating PPHN is inhaled nitric oxide (iNO).[24,36] Preterm infants with severe hypoxemia due to PPHN may benefit from iNO, especially in the presence of oligohydramnios and

ruptured membranes. Additionally, the use of iNO can decrease the need for extracorporeal membrane oxygenation (ECMO) support in infants with PPHN, or in infants with an oxygenation index >25 and hypoxemic respiratory failure. To improve iNO efficacy in infants with PPHN secondary to parenchymal lung disease, "lung recruitment strategies" (eg, positive end-expiratory pressure)[36] should be used.[24]

The 2015 AHA/ATS guideline recommended that sildenafil can be used as an adjunct to iNO in infants who have refractory PPHN, particularly if the oxygenation index is >25 (*Class IIa*)[24]; a sildenafil formulation preference is not indicated in the recommendation.[24] Further guidance from expert opinion recommended that oral sildenafil can be used if iNO is unavailable, and IV sildenafil is preferred over the oral preparation in critically-ill infants.[34] An inhaled prostacyclin analog can also be used as adjunctive treatment for iNO-resistant PPHN in infants with an oxygenation index >25, but the guideline recommendation strength is lower (*Class IIb*).[24] According to expert consensus, IV prostanoids can also be considered, but they should be administered via a central venous line, and used cautiously due to the potential risk of adverse events.[34]

Infants (near-term or at term) with severe PH or hypoxemia who are iNO non-responders, and who fail to achieve an adequate response to pharmacotherapy should receive ECMO support.[24] Milrinone, a vasodilator with positive inotropic effects,[36] may be considered in infants with PPHN who have evidence of left ventricular dysfunction.[24] Additionally, surfactant can be considered for infants with PPHN due to parenchymal lung disease or meconium aspiration syndrome, with severe disease and inadequate lung recruitment (not a graded recommendation). If an infant with severe PAH continues to worsen while using conventional treatment modalities, including vasodilators, lung recruitment, or EMCO support, evaluation for other developmental lung disease (eg, genetic surfactant protein diseases) should be considered.[24]

Table 6 summarizes guideline recommendations for the treatment of pediatric PAH, including PPHN.

Table 6. Clinical Practice Guideline Recommendations for the Treatment of Pediatric PAH

2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension[3]	Recommendation Class, LoE
Children	
• For children with PAH, it is recommended to have an age-appropriate treatment plan based on the child's risk category and treatment response	**Class I, Level C**
• It is recommended to use acute vasoreactivity testing in children with **IPAH/HPAH** to identify whether CCBs may be beneficial	**Class I, Level C**
• Acquiring a low-risk category, as well as sustaining the lower-risk profile is considered a sign of a positive treatment response in children with PAH	**Class IIa, Level C**
• Response to treatment should be based on a culmination of information obtained from echocardiographic findings, biomarker levels, clinical evaluation, and exercise tests	**Class I, Level C**
Infants	
• Given that pulmonary hypertension in neonates and infants is often due to developmental lung disease (ie, vascular or parenchymal), a customized diagnostic and therapeutic approach, different from older children and adults, can be considered	**Class IIa, Level C**
2015 AHA/ATS Guideline on Pediatric Pulmonary Hypertension[24]	
Conventional Background Treatment for Select Patients	
• Diuretics (eg, hydrochlorothiazide, furosemide, spironolactone) and digoxin can be considered for pediatric patients if signs of right heart failure exist, but should be initiated cautiously	**Class IIb, Level C**
• Long-term warfarin use can be considered for pediatric patients with IPAH or HPAH, those with a reduced cardiac output, those predisposed to hypercoagulable disorders, or those with a chronic indwelling catheter	**Class IIb, Level C**
○ General INR goal of warfarin is within the range of 1.5 to 2.0	**Class I, Level C**

2022 ESC/ERS and 2015 AHA/ATS Guidelines: ***Recommendation Class****: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention should be considered; Class IIb, the intervention may be considered; Class III, the intervention is not recommended.* ***Level of Evidence****: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on large non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, and/or retrospective studies, case studies, small studies, registries, standard of care.*

Abbreviations: ACD, alveolar capillary dysplasia; AHA, American Heart Association; ATS, American Thoracic Society; CCBs, calcium channel blockers; ECMO, extracorporeal membrane oxygenation; ERS, European Respiratory Society; ESC, European Society of Cardiology; HPAH, heritable pulmonary arterial hypertension; iNO, inhaled nitric oxide; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; LoE, level of evidence; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary veno-occlusive disease; TID, three times per day; WHO-FC, World Health Organization functional class

Table 6. Clinical Practice Guideline Recommendations for the Treatment of Pediatric PAH

○ Anticoagulation should be avoided in young children with PAH due to the potential risk of hemorrhagic complications	**Class III, Level C**
• Supplemental oxygen can be considered for pediatric patients with PAH if their oxygen saturation is below 92%; this may be particularly beneficial for patients with PAH due to an underlying respiratory condition	**Class IIa, Level B**
Calcium Channel Blockers (CCBs)	
• CCBs are recommended only for patients who had a positive response to AVT and who are at least 1 year of age	**Class I, Level C**
• CCBs are contraindicated in pediatric patients who have not had, or did not respond to AVT, and in patients who suffer from right-sided heart failure (ie, WHO-FC IV)	**Class III, Level C**
• Ideally, ER preparations of nifedipine and diltiazem should be used	**Class I, Level B**
• Dosing of oral CCBs in pediatric patients: ○ Starting doses: nifedipine 0.1 to 0.2 mg/kg TID; diltiazem 0.5 mg/kg TID; amlodipine 0.1 to 0.3 mg/kg/day ○ Target doses: nifedipine 2 to 3 mg/kg/day; diltiazem 3 to 5 mg/kg/day; amlodipine 2.5 to 7.5 mg daily	
PAH-specific Treatment	
Lower-Risk Patients With PAH	
• Children who are at lower risk should be initiated on an oral ERA or PDE5 inhibitor	**Class I, Level B**
• As a goal-oriented approach, it may be helpful to add PAH-specific agents in a manner to achieve individualized clinical goals or therapeutic values	**Class IIa, Level C**
Higher-Risk Patients With PAH	
• Pediatric patients who are higher-risk should be immediately initiated on SC or IV prostacyclin analogs	**Class I, Level B**
○ Asymptomatic pediatric patients with PAH can be transitioned from SC or IV agents to inhaled or oral agents if they have shown continual, near-normal pulmonary hemodynamic parameters	**Class IIb, Level C**

2022 ESC/ERS and 2015 AHA/ATS Guidelines: ***Recommendation Class****: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention should be considered; Class IIb, the intervention may be considered; Class III, the intervention is not recommended.* ***Level of Evidence****: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on large non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, and/or retrospective studies, case studies, small studies, registries, standard of care.*

Abbreviations: ACD, alveolar capillary dysplasia; AHA, American Heart Association; ATS, American Thoracic Society; CCBs, calcium channel blockers; ECMO, extracorporeal membrane oxygenation; ERS, European Respiratory Society; ESC, European Society of Cardiology; HPAH, heritable pulmonary arterial hypertension; iNO, inhaled nitric oxide; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; LoE, level of evidence; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary veno-occlusive disease; TID, three times per day; WHO-FC, World Health Organization functional class

Table 6. Clinical Practice Guideline Recommendations for the Treatment of Pediatric PAH

▪ Transitioning from parenteral to inhaled or oral preparations should be conducted in specialized pediatric PH centers; the patient should be frequently monitored during the transition	**Class I, Level B**
Additional Considerations for Patients with Certain PAH Subsets	
IPAH	
• The following pediatric patients should be referred for further evaluation at a lung transplantation center:	**Class I, Level A**
○ Those who are WHO-FC III or IV despite receiving optimized medical interventions	
○ Those with a rapidly progressive disease	
○ Those who have PVOD	**Class I, Level B**
○ Those with confirmed pulmonary capillary hemangiomatosis	
PPHN	
• To decrease the need for ECMO support in infants (near-term or at term) with PPHN, or in infants with an oxygenation index >25 and hypoxemic respiratory failure, iNO should be used	**Class I, Level A**
○ Preterm infants with severe hypoxemia due to PPHN may benefit from iNO, especially in the presence of oligohydramnios and ruptured membranes	**Class IIb, Level B**
○ Sildenafil (Class IIa, Level B) or inhaled prostacyclin analogs (Class IIb, Level B) can be used as adjunctive treatment in infants with iNO-resistant PPHN, particularly if the oxygenation index is >25	**Class IIa/b, Level B**
• In infants with PPHN secondary to parenchymal lung disease, "lung recruitment strategies" should be used to improve iNO efficacy	**Class I, Level B**
• "ECMO support is indicated for term and near-term neonates with severe PH or hypoxemia that is refractory to iNO and optimization of respiratory and cardiac function"[24] (page 2042)	**Class I, Level A**

2022 ESC/ERS and 2015 AHA/ATS Guidelines: ***Recommendation Class****: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention should be considered; Class IIb, the intervention may be considered; Class III, the intervention is not recommended.* ***Level of Evidence****: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on large non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, and/or retrospective studies, case studies, small studies, registries, standard of care.*

Abbreviations: ACD, alveolar capillary dysplasia; AHA, American Heart Association; ATS, American Thoracic Society; CCBs, calcium channel blockers; ECMO, extracorporeal membrane oxygenation; ERS, European Respiratory Society; ESC, European Society of Cardiology; HPAH, heritable pulmonary arterial hypertension; iNO, inhaled nitric oxide; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; LoE, level of evidence; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary veno-occlusive disease; TID, three times per day; WHO-FC, World Health Organization functional class

Table 6. Clinical Practice Guideline Recommendations for the Treatment of Pediatric PAH

• For infants with severe PAH who have not improved with vasodilator treatment, lung recruitment, or EMCO support, should be evaluated for other developmental lung diseases (eg, genetic surfactant protein diseases, ACD)	**Class IIa, Level B**
• Infants with PPHN and evidence of left ventricular dysfunction can be considered for IV milrinone	**Class IIb, Level B**

2022 ESC/ERS and 2015 AHA/ATS Guidelines: ***Recommendation Class****: Class I, the intervention is recommended; Class II, there is conflicting evidence, disagreement among opinions, or both regarding the therapeutic utility/effectiveness of the intervention; Class IIa, intervention should be considered; Class IIb, the intervention may be considered; Class III, the intervention is not recommended.* ***Level of Evidence****: Level A, based on multiple meta-analyses or randomized controlled trials; Level B, based on large non-randomized studies (eg, cohort studies, observational studies, case-control studies) or a single randomized controlled trial; Level C, based on consensus expert opinion, and/or retrospective studies, case studies, small studies, registries, standard of care.*

Abbreviations: ACD, alveolar capillary dysplasia; AHA, American Heart Association; ATS, American Thoracic Society; CCBs, calcium channel blockers; ECMO, extracorporeal membrane oxygenation; ERS, European Respiratory Society; ESC, European Society of Cardiology; HPAH, heritable pulmonary arterial hypertension; iNO, inhaled nitric oxide; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; LoE, level of evidence; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary veno-occlusive disease; TID, three times per day; WHO-FC, World Health Organization functional class

7.0 OTHER USES FOR PAH-SPECIFIC AGENTS§

Although a comprehensive review of PH disorders other than Group 1 (PAH) was outside the scope of this report, recommendations from the 2015 AHA/ATS guideline regarding the use of PAH-specific drugs for other groups of PH are listed below:

- Infants with PH and bronchopulmonary dysplasia (BPD), with underlying cardiac and respiratory disease(s) appropriately treated with optimized therapy, may benefit from PAH-specific agents (Class IIa, Level C)
- Pediatric patients should receive inhaled prostacyclin analogs, iNO, or both, as initial, add-on treatment to conventional postoperative management for pulmonary hypertension crises and right-sided heart failure (Class I, Level B)
- "Sildenafil should be prescribed to prevent rebound PH in patients who have evidence of a sustained increased in PAP on withdrawal of iNO and require reinstitution of iNO despite gradual weaning of iNO dose"[24] (page 2046) (Class I, Evidence B)
- Patients with confirmed PH (indicated as a significant increase in PVR and non-elevated pulmonary capillary wedge pressure, as measured by cardiac catheterization) and sickle cell disease, may be considered for PAH-specific agents (Class IIb; Level C)
    - Patients with sickle cell disease and significantly increased PVR should try an ERA or prostacyclin analog before a PDE5 inhibitor (Class IIa, Level B)
    - Empiric treatment with a PAH-specific agent is not recommended in patients with PH secondary to sickle cell disease (Class III, Level C)

Inhaled formulations of treprostinil are also FDA-approved for improving exercise ability in patients with PH secondary to interstitial lung disease (Group 3 PH).[18,19]

7.1 Off-label Uses of PAH-specific Agents

Table 7 summarizes the off-label uses for PAH-specific agents in pediatric and adult patients, as indexed in the drug compendia: Micromedex and Lexicomp. Only non-FDA approved indications indexed as "effective" or "evidence favors efficacy" were extracted from Micromedex. According to Lexicomp, some off-label uses are recommended in clinical guidelines; however, all of the listed off-label uses indexed in Lexicomp pertain to the adult population. The only **pediatric**, off-label use indexed in Micromedex for these agents is for sildenafil, for the treatment of PPHN; the supportive evidence for efficacy, rated *Category B*, is based on RCTs with critical limitations (eg, bias), meta-analyses of RCTs with conflicting results, or non-randomized studies.[42] As previously mentioned, this agent is recommended in the 2015 AHA/ATS guideline as adjunctive treatment for PPHN in infants.[24]

The following PAH-specific agents had no off-label indications for pediatric or adult patients listed in the drug compendia, Micromedex or Lexicomp[43-48]: ambrisentan, treprostinil, macitentan, selexipag, and riociguat.

§ Refer to the Drug Utilization Review (DUR) report on adult pulmonary arterial hypertension (PAH), completed March 2023, for guideline recommendations for adults regarding the use of PAH-specific agents for other groups of pulmonary hypertension. Available at: https://medicaid.utah.gov/pharmacy/drug-utilization-review-board/

Table 7. Off-label Indications for PAH-specific Agents

Active Ingredient	Micromedex[a]	Lexicomp[b]
Pediatric Off-Label Indication(s)		
Sildenafil[42,49]	*Evidence favors efficacy (Category B):* • Persistent pulmonary hypertension of the newborn	--
Adult Off-Label Indication(s)		
Epoprostenol[50,51]	*Effective (Category B):* • Angina pectoris • Acute vasodilator testing in pulmonary hypertension *Evidence favors efficacy (Category B):* • Cardiopulmonary bypass surgery with pulmonary hypertension • Hemodialysis • Transplant of kidney pretreatment *Evidence favors efficacy (based on case report)*: • Eisenmenger's syndrome	• Acute vasodilator testing in pulmonary hypertension (LoE G) • Refractory, moderate to severe acute respiratory distress syndrome (LoE C) • Development of pulmonary hypertension, refractory hypoxemia, or right ventricular dysfunction following heart surgery (LoE B)

[a] *Only non-FDA approved indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed only in the "In-depth Answers" view of the database*

***Micromedex categories for the strength of evidence**:*

- *Category A: based on consistent results from meta-analyses of randomized controlled trials (RCTs) or several well-conducted, large RCTs*
- *Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies*
- *Category C: based on expert consensus or opinion, case series or case reports*

[b] ***Lexicomp level of evidence:***

- *B: "Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate."[47] (Level of Evidence Definitions)*
- *C: "Evidence from observational studies (eg, retrospective case series/ reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials(eg, when limited options exist for condition). Any estimate of effect is uncertain."[47] (Level of Evidence Definitions)*
- *G: "Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline."[47] (Level of Evidence Definitions)*

Abbreviations: LoE, level of evidence; PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class

Table 7. Off-label Indications for PAH-specific Agents

Active Ingredient	Micromedex[a]	Lexicomp[b]
Iloprost[52,53]	*Evidence favors efficacy (Category B):* • Acute kidney injury after receiving contrast media; prophylaxis • Transient osteoporosis	• Acute vasodilator testing in pulmonary hypertension (LoE C, G)
Bosentan[54,55]	*Evidence favors efficacy (Category B):* • Eisenmenger's syndrome (WHO-FC III PAH)	• Digital ulcers in systemic sclerosis (LoE B, G) • Raynaud's phenomenon in systemic sclerosis (LoE C)
Sildenafil[42,49]	*Evidence favors efficacy:* • Erectile dysfunction: various drug-induced, or disease- or surgical-related etiologies (see Micromedex; *Category A to C*) • Female sexual arousal disorder *(Category B)* • Secondary Raynaud's phenomenon *(Category B)* • Sexual dysfunction: antidepressant drug adverse reaction *(Category B)*; spinal cord injury *(Category B)*	• High-altitude pulmonary edema (LoE G) • Raynaud's phenomenon (LoE B, G)
Tadalafil[56,57]	*Evidence favors efficacy (Category B):* • Secondary Raynaud's phenomenon	• High-altitude pulmonary edema (LoE G)

[a] *Only non-FDA approved indications indexed as "effective" or "evidence favors efficacy" were extracted; some off-label uses are displayed only in the "In-depth Answers" view of the database*

***Micromedex categories for the strength of evidence**:*

- *Category A: based on consistent results from meta-analyses of randomized controlled trials (RCTs) or several well-conducted, large RCTs*
- *Category B: based on meta-analyses of RCTs with conflicting results, RCTs with critical limitations (eg, bias, small sample size), or non-randomized studies*
- *Category C: based on expert consensus or opinion, case series or case reports*

[b] ***Lexicomp level of evidence:***

- *B: "Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate."[47] (Level of Evidence Definitions)*
- *C: "Evidence from observational studies (eg, retrospective case series/ reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials(eg, when limited options exist for condition). Any estimate of effect is uncertain."[47] (Level of Evidence Definitions)*
- *G: "Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline."[47] (Level of Evidence Definitions)*

Abbreviations: LoE, level of evidence; PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class

8.0 SUPPLEMENTAL PEDIATRIC RANDOMIZED CONTROLLED TRIALS

To supplement the evidence in the 2022 ESC/ERS guideline[3] for PAH-specific agents used in pediatric patients (**Table 8**), we screened systematic reviews (SRs) to determine if additional RCTs were available. If no pediatric RCTs were found in the SRs for a particular agent, a supplemental RCT search was performed; the dates of the searches for each agent were restricted based on available evidence in SRs (see **Appendix B** for the search strategies). Information from these searches are summarized in the following subsections. The information in these subsections is not comprehensive, but provides additional insight into the level of higher-quality evidence available for PAH-specific agents used in the pediatric population affected with PH.

Table 8. Evidence for PAH-specific Agents in Pediatric Patients with Pulmonary Hypertension

Active Ingredient Formulation	**Study Design in Pediatric Patients**	
	2022 ESC/ERS Guideline[3] Review	**Our Review[a]**
Prostacyclin Analogs		
Epoprostenol Intravenous	Retrospective cohort studies	No RCTs found
Iloprost Inhalation	• Insufficient evidence • Small, retrospective case series	RCTs found for postoperative pulmonary hypertension
Treprostinil[b] Intravenous Subcutaneous	Retrospective cohort studies	RCT found for PAH associated with congenital heart disease
Endothelin Receptor Antagonists		
Ambrisentan Oral	Uncontrolled, open-label trial	No RCTs found
Bosentan Oral	Uncontrolled, open-label studies	RCTs found for persistent pulmonary hypertension of the newborn
Macitentan Oral	• Insufficient evidence • Ongoing, open-label study	RCT found for Eisenmenger syndrome, a PAH-related congenital heart defect
Phosphodiesterase Type 5 Inhibitors		
Sildenafil Oral	Randomized, open-label controlled trial	SRMA of RCTs found for PAH
Tadalafil Oral	Randomized, open-label controlled trial	No additional RCTs found

[a] *Our evidence review for RCTs was based on screening a couple SRs and is not comprehensive*

[b] *Study designs for the inhaled and oral formulations of treprostinil in pediatric patients were not listed in the 2022 ESC/ERS guideline*

Abbreviations: ERS, European Respiratory Society; ESC, European Society of Cardiology; PAH, pulmonary arterial hypertension; RCTs, randomized controlled trials; SRMA, systematic review meta-analysis

8.1 Phosphodiesterase Type 5 Inhibitors

Sildenafil: The use of sildenafil to treat pediatric PAH is controversial based on the results from a long-term, dose-ranging, extension study of an RCT, STARTS-2.[22] Despite oral sildenafil showing efficacy (with medium or high dosages) for the treatment of pediatric PAH in the previous RCT (STARTS-1),[58] the STARTS-2 extension uncontrolled study propagated concerns about higher doses of sildenafil (ie, 20–80 mg three times daily [TID] depending on weight as compared to 10 mg TID) increasing the risk of mortality in children with PAH.[21] The STARTS-2 trial suffered from serious flaws in its study design and survival analysis (eg, lack of adjustment for sildenafil dose up-titration, no placebo comparator, and missing outcome data).[59] Nevertheless, findings from the STARTS-2 trial potentially contributed to the differences in the approved age for use of this agent in the US and Europe. In the US, sildenafil is only approved for the treatment of PAH in adults[21] whereas in Europe, sildenafil is approved to treat PAH in children as young as 1 year of age.[3]

According to a 2020 systematic review meta-analysis (SRMA) of RCTs, sildenafil significantly reduced mortality in pediatric patients with PAH compared to controls (relative risk: 0.25, 95% confidence interval [CI] 0.12 to 0.51).[23] Importantly, the subgroup analyses regarding the mortality rate between the low- and high-dose sildenafil groups was not significantly different; authors separated low-and high-dose groups based on a threshold dose of 2.4 mg/kg/day. Notably, this SRMA did not include the STARTS-1 trial, and the etiologies for PAH varied across included studies, but primarily consisted of PPHN and CHD.[23] In contrast, the STARTS-2 uncontrolled trial included approximately 1/3 of patients with IPAH/HPAH, and the remainder with CHD (repaired or unrepaired).[22] Oral sildenafil was evaluated in the STARTS-2 trial[22] and in all but one of the included studies in the SRMA.[23]

Tadalafil: No RCTs, aside from the phase 3 RCT[60] cited in the 2022 ESC/ERS guideline,[3] were identified for tadalafil for the treatment of pediatric PAH.

8.2 Endothelin Receptor Antagonists

Bosentan: Several pediatric, uncontrolled[61-63] or randomized[64] open-label studies have been conducted for bosentan,[65] leading to FDA-approval in children ≥3 years of age with idiopathic or congenital PAH.[8] In addition, we identified the following RCTs:

- Two RCTs evaluated bosentan, either as monotherapy[66] or as adjunct to iNO,[67] in the treatment of PPHN. One RCT showed that bosentan was more effective than placebo at demonstrating a favorable response,[66] but the other showed that it was not better than placebo in improving time to weaning from iNO or mechanical ventilation.[67]
    - The comparable result to placebo may have been influenced by the higher disease severity of patients in the bosentan group relative to the placebo group.[67]
- Another RCT suggested that bosentan is at least as effective as sildenafil at treating PPHN in neonates.[68]

Ambrisentan: No RCTs were identified for ambrisentan for the treatment of pediatric PAH.

Macitentan: The use of macitentan has been evaluated in a phase 3 RCT among patients ≥12 years of age with WHO-FC II to III and Eisenmenger syndrome, a severe congenital heart defect associated with PAH.[69] Out of the total study population (N=226), 15 participants were between the ages of 12−17 years, and the remaining population consisted of adults, mostly between 18−55 years of age. Patients were able to continue background treatment for PAH. Macitentan 10 mg daily did not produce a significant difference compared to placebo in exercise capacity (as measured by the 6MWD test) from baseline to week 16 (primary endpoint). However, after 16 weeks of treatment, a greater proportion of patients showed improvement in WHO-FC with macitentan compared to placebo (14.3% vs. 8.8%, respectively), but the association between treatment and improvement was not statistically significant (odds ratio: 0.53, 95% CI 0.23 to 1.24). For exploratory end points, compared to placebo, macitentan significantly reduced NT-proBNP, and within a subgroup of patients, decreased pulmonary vascular resistance index (PVRI) from baseline to week 16. No overt concerns regarding safety were observed.[69]

8.3 Prostacyclin Analogs

A 2019 Cochrane SR did not find any completed neonatal RCTs evaluating prostanoid therapies for the treatment of PPHN.[70] However, another 2019 Cochrane SR found RCTs regarding the use of epoprostenol, treprostinil, iloprost, and beraprost for the treatment of PAH in children and adults.[71] While the enrollment criteria for some of the included RCTs specified pediatric-aged patients, the majority of enrolled patients were adults,[71] based on the mean demographic age.[72-78] Overall, participants who received a prostacyclin analog (ie, epoprostenol, treprostinil, iloprost, beraprost) had significantly improved outcomes (eg, WHO-FC, 6MWD test, mortality, mPAP) compared to controls, and the treatment effect tended to be larger with the intravenous formulation.[71] Due to the uncertain generalizability of the results to pediatric patients, we performed a tailored search to identify RCTs evaluating epoprostenol, treprostinil, or iloprost for the management of pediatric PAH.

Epoprostenol: No RCTs were identified for epoprostenol for the treatment of pediatric PAH.

Treprostinil: An RCT among children with PAH-CHD showed intravenous (IV) treprostinil significantly improved pulmonary and hemodynamic parameters after cardiopulmonary bypass surgery compared to controls (ie, normal saline).[79]

Iloprost: Iloprost has been evaluated in pediatric RCTs regarding the management of postoperative pulmonary hypertension following congenital heart surgery, showing a favorable benefit over placebo,[80] but not conventional treatment.[81] Additionally, 2 RCTs compared iNO to aerosolized iloprost in pediatric patients after undergoing cardiac surgery for the treatment of PH[82,83]; these RCTs showed that the treatments were similarly effective. Neither treatment was significantly better at improving post-surgical hemodynamic parameters,[83] or the frequency of perioperative pulmonary hypertensive crises within 72 hours post-surgery.[82]

9.0 SUPPLEMENTAL PEDIATRIC OBSERVATIONAL STUDIES

Ambrisentan: Although US product labeling for ambrisentan is labeled without an approved age for use in the treatment of PAH,[12] it is approved in Europe for this condition in children and adolescents aged 8

to <18 years[26] based on a phase IIb, open-label, uncontrolled trial (see note[**]), with patients randomized to 2 different doses of ambrisentan (low dose: 2.5−5 mg; high dose: 5−10 mg).[84] The primary outcome of the trial was to assess the safety of each dose in pediatric patients with PAH (N=41) over 6 months, either as monotherapy or combined with other background PAH agents from a differing drug class. Ambrisentan showed a favorable side effect profile in pediatric patients, which was consistent with results observed in previous adult controlled trials. Additionally, from baseline to week 24, ambrisentan improved exercise capacity, as measured by the duration of 6MWD test (secondary outcome), in both treatment groups, and the majority of participants experienced maintained or improved WHO-FC. Although the efficacy findings concur with the results observed in adults, the smaller sample size and uncontrolled design prohibits any definitive conclusions.[84]

Treprostinil: IV treprostinil has been evaluated in a pharmacokinetic substudy for the treatment of functional single-ventricle PAH in pediatric patients (N=36).[85] Compared to baseline, treprostinil significantly improved cardiopulmonary hemodynamic parameters (eg, mPAP, pulmonary-to-systemic arterial pressure ratio), without any serious infusion site reactions (eg, erythema, rash) or adverse events reported.[85]

Riociguat: A recent pharmacokinetic and safety study of riociguat, a soluble guanylate cyclase stimulator, was conducted among pediatric patients aged 6 to 17 years to assess its suitability as a treatment option for PAH (NCT02562235).[86] Observational results showed that riociguat was generally well tolerated and drug plasma concentrations in pediatric patients were similar to those reported in previous adult trials. Riociguat was observed to have positive, albeit modest, benefit from baseline.[86] Future studies, including RCTs, may be needed to provide additional insights into the use of riociguat for pediatric PAH.

Selexipag: Currently, a phase 3 RCT is recruiting to assess the efficacy and safety of selexipag as add-on treatment among children aged 2−17 years with PAH (NCT04175600),[87] for which it has been previously studied in an observational study.[88] In this prospective, multicenter, uncontrolled observational study, oral selexipag, as add-on treatment, was evaluated in children with PAH (N=15) for a median of 8 months. Generally, selexipag was well tolerated, but responses varied, with less sick patients more likely to have a greater response; selexipag improved outcome-related parameters from baseline, including hemodynamics in approximately 50% of patients, and about 25% of patients were stabilized. Although no deaths occurred during the observational period, one patient, taking IV treprostinil, died 18 months following the completion of the study due to right ventricle failure.[88]

10.0 UTILIZATION DATA

PAH-specific agents with preferred status on the Utah Medicaid Preferred Drug List (PDL; March 1, 2023 version) are ambrisentan (generic), bosentan (brand Tracleer), sildenafil (generic), tadalafil (generic), and epoprostenol (generic); all other PAH agents/dosage forms are listed as non-preferred on the PDL.[89] Notably, preference changes on the PDL occurred from 2022 to 2023; for example, in 2022, Letairis was listed as preferred and ambrisentan as non-preferred, which may have played a role in the utilization of these agents.

[**] Due to the low number of participants, no formal statistical comparisons between treatment groups were made.

In 2022, 20 unique pediatric patients (<18 years of age) had a prescription filled for a PAH-specific agent. The most utilized PAH-specific agent was sildenafil (69% of total claim counts over 1 year: 37% for the oral tablet; 32% for the oral suspension). Agents with lower utilization by claims were tadalafil (19%), ambrisentan (brand Letairis, 7%), and bosentan (brand Tracleer, 3%). There were no pediatric pharmacy claims for epoprostenol, iloprost, treprostinil, macitentan, selexipag, and riociguat, and no pediatric medical claims for any PAH-specific agent of interest. **Table 9** shows the pharmacy utilization data for PAH-specific agents within the Medicaid fee-for-service (FFS) pediatric population.

Table 9. 2022 Medicaid FFS Pharmacy Claims Among Pediatric Patients (<18 years of age)

Active Ingredient	Product	Patients	Claims
Ambrisentan	Letairis 5 mg oral tablet	<5	11
Bosentan	Tracleer 32 mg oral tablet	<5	5
Sildenafil Citrate	Sildenafil 10 mg/mL oral suspension	8	47
	Sildenafil 20 mg oral tablet	7	53
Tadalafil	Tadalafil 5 mg oral tablet	<5	13
	Tadalafil 20 mg oral tablet	<5	15
Total		**20**	**144**

[a] *In the claims database, product formulations were indexed for the treatment of pulmonary hypertension; these formulations are distinct from those used to treat erectile dysfunction*

Abbreviations: FFS, fee-for-service

11.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION CRITERIA

Utah Medicaid currently has prior authorization (PA) criteria in place for the treatment of PAH (updated June 2022; see **Appendix A**), and pertains to the following agents:

- **Prostacyclin pathway agonists:** Flolan (epoprostenol), Orenitram (treprostinil), Remodulin (treprostinil), Tyvaso (treprostinil), Uptravi (selexipag), Veletri (epoprostenol), and Ventavis (iloprost)
- **Endothelin receptor antagonists:** Letairis (ambrisentan), Opsumit (macitentan), and Tracleer (bosentan)
- **Nitric oxide-cGMP enhancers:** Adcirca (tadalafil), Adempas (riociguat), Alyq (tadalafil), and Revatio (sildenafil)

Agents listed on the PA form are FDA-approved for the treatment of PAH, but only bosentan (Tracleer) is explicitly approved for use in the pediatric population (children ≥3 years of age; see note[††]).[8] Except for sildenafil and riociguat (approved for adults only),[21,90] other agents are labeled more generally without a specified age for use.[9-20]

[††] Agents that are approved in Europe for the treatment of PAH in children include sildenafil (≥1 year of age), bosentan (≥1 year of age), and ambrisentan (≥8 years of age).[3,25]

In the March 2023 Drug Utilization Review (DUR) report *Approved Therapies for the Treatment of Pulmonary Arterial Hypertension in Adults*, the Drug Regimen Review Center (DRRC) proposed several clarifications or modifications to the existing PA criteria (see **Appendix A**).[91] The criteria listed below for pediatric PAH (A through F) is generally consistent with those proposed modifications. However, a few additional details specific to pediatric patients must also be considered:

A. *Medication must be prescribed by, or in consultation with a pulmonologist or cardiologist*
   - Reviewed guidelines recommended that pediatric care for PH should occur in specialized PH centers (see note[‡‡]), preferably those experienced in pediatric management, by a multidisciplinary team.[3,24] As written on the PA form, a variety of specialized medical providers (cardiologists or pulmonologists) are able to appropriately prescribe treatment for PAH, which seems reasonable given that not all Utah Medicaid members may have access to a specialized PH center.

B. *Diagnosis of PAH, confirmed by right heart catheterization in adults, with documentation of mean pulmonary arterial pressure (mPAP)*
   - Similar to adults, the gold standard for diagnosing PH in children is right heart catheterization (RHC),[3] with the exception of PPHN (a subset of PAH). In children with PH, cardiac catheterization can cause serious complications, especially for patients who are in a worse clinical state (eg, WHO-FC IV) or are young infants.[3] Therefore, it may be appropriate to delay or not perform heart catheterization in certain patient scenarios where the risk outweighs the benefit.
     - The gold standard for diagnosing PPHN is echocardiography.[3,33,38] It appears RHC may have limited utility, or may even be contraindicated,[39] in infants with suspected PPHN.[3]
   - Documentation of mPAP upon initial diagnosis can be helpful to determine whether treatment-naïve patients would be considered to have PH, defined as a mPAP >20 mmHg.[3] To identify *pediatric* pre-capillary PH (which is characteristic of PAH and some other types of PH), additional criteria of a pulmonary vascular resistance index (PVRI) of ≥3 Woods units (WU)•m^2, and a pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg should be confirmed using RHC at a specialized PH center.[3,24] While hemodynamics can aid to distinguish PH, ultimately the diagnosis should be a culmination of all clinical findings, and reflect the entire clinical scenario.[3] Furthermore, PPHN is not defined by certain hemodynamic thresholds,[40] but rather clinical presentation (eg, hypoxemia) and echocardiography findings.

Consider having separate diagnostic criteria for PAH in pediatric patients and PPHN in infants. For PAH, diagnosis should be confirmed by RHC, and supported with a historical mPAP of >20 mmHg in treatment-naïve patients. If the patient is unable to undergo cardiac catheterization, the provider should state the reason with medical justification. For PPHN, diagnosis should be supported by echocardiography findings.

[‡‡] The Pulmonary Hypertension Association accredits specialized PH centers across the US; the list of accredited centers is available at: https://phassociation.org/phcarecenters/accredited-centers/. In Utah, two centers are listed, and both are specific to adult care; these centers are the Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Program at Intermountain Medical Center (Murray, UT), and the Pulmonary Hypertension Program at the University of Utah (Salt Lake City, UT). Nationally, there are 8 accredited pediatric specialty centers listed.

C. *Requirement for vasoreactivity testing and trial/failure of calcium channel blockers (titrated to maximum tolerated dosages)*

- As written on the PA form, it seems that all patients are required to have acute vasoreactivity testing (AVT), and must fail treatment with calcium channel blockers (CCBs) in order to receive coverage for agents approved for PAH. Yet, the newer guideline (2022 ESC/ERS) recommended AVT/CCBs only for certain subsets of pediatric PAH: IPAH and HPAH; these subsets are most likely to benefit from CCBs based on available evidence.[3] Guidelines recommended CCBs for children (at least 1 year of age)[24] with a positive response to AVT.[3,24] Pediatric patients who either are a) inappropriate for AVT or CCBs, or b) who showed an inadequate or non-sustained response to CCBs should be started on PAH-specific agents.[3,5,24] Examples in which pediatric patients are not candidates for CCBs (or in which treatment with CCBs may be considered inappropriate based on the provider's clinical judgement) include the following:
    - Patients who have not had, or did not respond to AVT
    - Patients who have PPHN
    - Patients who are younger than 1 year of age[24]
    - Patients with right-sided heart failure (ie, WHO-FC IV)[24]
    - Patients who have a PAH subtype where evidence for CCB therapy is lacking[3]
    - When the risks of performing AVT, and thus using CCBs are determined to be too high
        - Patients who are more likely to experience unfavorable outcomes during AVT are those with WHO-FC IV symptoms, low cardiac output, low systemic blood pressure, or pulmonary veno-occlusive disease.[41]

Consider having this requirement be for patients 1 year of age and older, and allowing provider attestation for cases that are inappropriate for AVT or CCBs. Alternatively, this criterion may be omitted.

D. *Patients must have WHO-FC of II, III, or IV*

- WHO-FC may be a helpful indicator of disease severity and treatment response, particularly in older children and adults. It should be considered that WHO-FC is dynamic and treated patients may improve to WHO-FC I. According to the guidelines, patients should continue treatment upon achieving a positive response (lower-risk category).[3] It is unclear if this criterion is required for members upon re-authorization; this recommendation can be disregarded if it is not required.
    - Current pharmacotherapies are not curative,[7,39] and chronic use is required to maintain a lower mortality risk. Additionally, patients with a WHO-FC I may require a switch in therapy to a different agent due to adverse reactions, tolerability, or administration burden (eg, switch from IV to oral therapy).
    - WHO-FC is a strong predictor of survival in pediatric patients and is used for setting treatment goals.[5] However, it may be particularly challenging to assign young children a WHO-FC due to the absence of exercise standards in children under 8 years of age, and the limited number of RCTs available for therapy guidance.[24]
    - The goal of therapy according to the 2022 ESC/ERS guideline is to achieve and maintain a low-risk status for poor prognosis of PAH, which is an indicator of a positive treatment response.[3] Besides WHO-FC, several risk factors contribute to the overall risk profile of

the patient, including serum biomarkers (NT-proBNP), signs of right ventricular failure, progression of symptoms, and hemodynamic parameters.[3]

- This criterion may prevent switches in PAH therapies, due to side effects or intolerability, while the patient has improved to WHO-FC I. Patients who are initiated on parenteral PAH agents during episodes of higher disease severity may eventually require a transition to oral therapy once they are in a stabilized condition of lower disease severity (eg, WHO-FC I or II).

Consider omitting this criteria for pediatric patients because WHO-FC assessment may not be suitable for young children. Additionally, it may limit the continual accessibility of PAH-specific agents for patients who have improved to WHO-FC I.

E. *Documentation of previous PAH-specific agents that have been tried **and failed**.*

- Presumably, this criterion aids in determining if a PDL preferred product has been tried and failed, allowing a non-preferred product to be tried. Currently, at least one agent from each drug class (ie, prostacyclin analogs, PDE5 inhibitors, ERAs) is preferred on the PDL. Alternatively, the provider can document medical necessity for the non-preferred product.
- Similar to adults, guidelines recommended monotherapy or combination therapy regimens of differing drug classes (ie, prostacyclin analogs, PDE5 inhibitors, or ERAs) for the treatment of PAH in pediatric patients.[3,5,24] If a drug regimen had an inadequate result, the individual agents themselves may not necessarily be considered "failed" because they can be tried in alternative regimens. It is unclear if the documentation of a "failed" agent would prevent coverage of that drug in the future (eg, unable to be used in future combination regimens).

Consider removing the wording "failed" from the PA form, and including a note that the documentation of a previously tried agent will not prevent coverage of that drug.

F. *To receive re-authorization (up to 6 months), the provider must show that the patient has had a positive response by either a 6-minute walk distance (6MWD) test or forced expiratory volume in 1 second (FEV_1), or adequate medical justification.*

- Because PAH-specific agents are not curative,[7,39] patients with PAH (except possibly PPHN)[34] require chronic, potentially life-long, use. If re-authorizations are not promptly executed, this may result in necessary treatment being abruptly discontinued; as a consequence, the patient may experience an exacerbation of symptoms and possibly hospitalization.
- The 6MWD test is used as a parameter to determine risk stratification of the patient, but this is only one of many assessments that are taken into consideration. Other factors include signs of right ventricular failure, progression of symptoms, WHO-FC, BNP or NT-proBNP levels, echocardiography findings, and hemodynamic parameters.[3] Ultimately, response to treatment should be based on a culmination of information obtained from echocardiographic findings, biomarker levels, clinical evaluation, and exercise tests.[3] Furthermore, the 6MWD test may not be age-appropriate for younger children (≤6 years of age).[5] FEV_1 is not included in either of the reviewed guidelines as an indicator of a positive PAH response.[3,24]
    - Although some of the PAH-specific agents are FDA-approved to improve exercise capacity or ability, numerous other beneficial outcomes (eg, delay disease progression, reduce clinical worsening) can be observed depending on the agent and formulation.[8-21]

- The 2015 AHA/ATS guideline recommended repeat cardiac catheterizations within 3 to 12 months after starting treatment to determine treatment response, or with clinical deterioration (*Class I; Level of Evidence B*).[24] However, the newer ESC/ERS guideline described that "…indications for repeated RHC in children with PH are currently not well defined."[3] (page 79)
- According to treatment algorithms for PAH, if clinical symptoms persist or worsen, patients may require add-on therapy from a different drug class, while continuing other therapies (ie, previously initiated mono- or dual therapy).[5,24]

Consider removing the criterion for re-authorization, or including additional markers for improved disease severity; the 6MWD test is not suitable for all children, especially those who are younger, and does not consider the whole clinical perspective. Additionally, reviewed guidelines do not include FEV_1 as an indicator of positive response for PAH. Re-authorization may be considered for removal altogether to prevent interruptions in treatment, or alternatively, extending the re-authorization period to every 9 or 12 months may be considered.

11.1 Additional Considerations

The 2015 AHA/ATS guideline and the pharmacy compendium Micromedex both support the off-label use of sildenafil to treat PPHN.[24,42] While there are available pediatric RCTs for off-label uses with other PAH-specific agents (tadalafil, bosentan, treprostinil, iloprost, macitentan),[60,66,67,69,79-83] no other pediatric off-label indications were indexed in Micromedex or Lexicomp for these agents (see **Table 7**). Although riociguat and selexipag are used in the management of adult PAH, both agents lacked evidence for safe and effective use in pediatric patients at the time of the 2022 ESC/ERS guideline's evidence review.[3]

Consider allowing the provider to submit a PA request for an off-label indication if it is supported by treatment guidelines, indexed in a recognized pharmacy compendium (eg, Micromedex, Lexicomp), or both.

Riociguat and the inhaled formulations of treprostinil (Tyvaso, Tyvaso DPI) are FDA-approved for additional indications aside from PAH[18,19,90]:

- Riociguat is also approved for improving exercise capacity and WHO-FC in adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH; Group 4 PH) after surgical intervention, or inoperable CTEPH
- Tyvaso and Tyvaso DPI are also approved for improving exercise ability in patients with PH secondary to interstitial lung disease (Group 3 PH)

"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."[91] (page 32)

Individuals who are already established on a PAH-specific drug regimen before receiving Utah Medicaid coverage may qualify for an exception (ie, grandfather clause) from having to undergo a new RHC and/or switching to preferred drugs on the PDL. To allow for the continuation of the patient's

established PAH therapy, an attestation field may be incorporated on the PA form enabling the provider to express previously initiated regimens that the patient had started with another payer.

12.0 SUMMARY

Pulmonary arterial hypertension (PAH), a rare and progressive disease affecting adults and children,[3] is characterized by increased pulmonary arterial pressure and pulmonary vascular resistance (PVR).[1,2] The predominant etiologies in children are idiopathic PAH (IPAH), heritable PAH (HPAH), and PAH due to irreversible congenital heart disease (PAH-CHD).[3,5,6] The majority of pediatric PAH cases occur in infants (82%), and these cases tend to be transient, diagnosed as either repairable cardiac shunt defects, or persistent pulmonary hypertension of the newborn (PPHN; a subset of PAH).[3] Ideally, pediatric PAH patients should receive care from centers with sufficient experience, specialized knowledge, and multidisciplinary teams for effective management.[1] Before targeted PAH treatments became available, survival from time of diagnosis in children with IPAH was typically 1−2 years.[24] Recently, the prognosis of children with PAH has improved considerably, primarily due to the increased availability of targeted PAH treatments[6]; currently, the predicted five-year survival rate is approximately 60% to 75% for some pediatric patients with certain PAH subsets.[1] If left untreated, PAH progresses into right ventricular heart failure, and eventual death.[7]

The treatment of pediatric PAH is based on limited evidence, as most randomized controlled trials (RCTs) have been limited to adults.[24] Consequently, guideline-recommendations are based on extrapolation from adult studies and supplemented by evidence from observational studies of children with PAH.[3]

The recommended treatment for pediatric PAH consists of conventional heart failure treatment, high-dose calcium channel blockers (CCBs), and/or PAH-specific agents: prostacyclin analogs, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors.[3,24] Generally, standard heart failure treatments such as digoxin, diuretics, warfarin, and oxygen can be considered, but their implementation should be tailored to individual patients' needs.[5] High-dose, oral CCBs should only be used in patients with a positive response to acute vasodilator testing (AVT),[5,24] who are at least 1 year of age, and who do not have contraindications (ie, right-sided heart failure).[24] The 2022 ESC/ERS guideline recommended AVT (and thus CCB use) only for pediatric patients with specific subtypes of PAH: IPAH or HPAH.[3] Pediatric patients who maintain a clinical improvement can continue CCB treatment, but those who experience a clinical decline may require repeat assessments and add-on treatment with PAH-specific agents.[5] Risk stratification for poor prognosis (see **Table 3**) is used to guide treatment decisions with respect to initiating PAH-specific monotherapy and combination regimens.[3,5,24]

Recommended *initial* treatment for *lower-risk* pediatric PAH patients is oral monotherapy with either an ERA (bosentan or ambrisentan) or PDE5 inhibitor (tadalafil or sildenafil).[5,24] Early combination treatment with an inhaled prostacyclin analog (treprostinil or iloprost) may also be beneficial in these patients, especially those who experience clinical worsening.[5]

Higher-risk pediatric patients should be immediately initiated on a subcutaneous (SC) or intravenous (IV) prostacyclin analog (treprostinil or epoprostenol).[5,24] The 2015 AHA/ATS guideline recommended considering transitioning from parenteral to inhaled or oral preparations when patients improve to an asymptomatic status with continual, near-normal pulmonary hemodynamic parameters.[24] Lung

transplant and interventional palliative surgery (eg, atrial septostomy, Potts shunt) should be considered in higher-risk patients who experience clinical worsening despite optimal medical[5] and pharmacological interventions.[3,5]

For the management of PPHN, the 2015 AHA/ATS guideline recommended sildenafil as an adjunct to inhaled nitric oxide (iNO) in infants who have refractive PPHN, particularly if the oxygenation index is >25.[24] A preference for any sildenafil formulation was not specified. According to expert opinion, oral sildenafil can be used if iNO is unavailable, and IV sildenafil is preferred over the oral preparation in critically-ill infants.[34] An inhaled prostacyclin analog can also be used as adjunctive treatment for iNO-resistant PPHN in infants with an oxygenation index >25, but the guideline recommendation strength is lower than the recommendation for sildenafil.[24]

The 2022 ESC/ERS guideline recommended that an age-appropriate treatment plan be based on the child's risk category and treatment response.[3] Generally, a positive treatment response is defined as achieving and maintaining the patient in a low-risk status (for poor prognosis). Although this is the ideal response, individualized treatment goals should be made because achieving a low-risk profile is not always feasible.[3] Assessment of treatment response should be based on a culmination of information obtained from echocardiographic findings, biomarker levels, clinical evaluation, and exercise tests.[3]

The only reviewed agent specifically FDA-approved for use in pediatric patients (≥3 years of age) is bosentan (Tracleer)[8]; whereas most other agents are labeled without a specified age for use.[9-20] Sildenafil is approved for adults only,[21] partially because a long-term, dose-ranging, extension, uncontrolled phase of a lead-in RCT (STARTS-2)[22] found that higher dosages of sildenafil were associated with an increased risk of mortality in pediatric patients with PAH.[21] However, a 2020 systematic review meta-analysis (SRMA) of RCTs showed that sildenafil significantly reduced mortality in pediatric patients with PAH compared to controls, and that the mortality rate between the low- and high-dose sildenafil groups (below or above 2.4 mg/kg/day) was not significantly different.[23]

Of the reviewed PAH-specific agents, only sildenafil has an off-label pediatric indication in Micromedex (for the treatment of PPHN); the evidence favors efficacy.[42] In the reviewed SRs, sildenafil tends to be commonly studied in pediatric patients with PAH, particularly for PPHN.[23,92-94] Other agents with RCT evidence for pediatric patients include tadalafil, bosentan, macitentan, treprostinil, and iloprost[60,66,67,69,79-83]; however, no pediatric off-label indications were indexed in Micromedex or Lexicomp for these agents (see **Table 7**). Although riociguat and selexipag are used in the management of adult PAH, at the time of the 2022 ESC/ERS guideline's evidence review, there was insufficient evidence to provide recommendations for or against their use in pediatric PAH.[3]

Specific considerations are provided for updates to the June 2022 Utah Medicaid prior authorization (PA) criteria for appropriate use of PAH-specific agents in pediatric patients (see **Section 11.0**). Proposed considerations are based on the reviewed guidelines and take into account off-label uses listed in recognized pharmacy compendia. The majority of the existing criteria require additional or alternative considerations for pediatric patients, including considerations for infants with PPHN; exempting right heart catheterization (RHC) when it may be an inappropriate diagnostic criterion; CCB candidacy (or lack of) for certain PAH subgroups, or CCB/vasoreactivity testing contraindications; treatment-experienced patients to maintain improved clinical status; and multi-parameter and age-appropriate assessments for pediatric patients.

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APPENDIX A: PRIOR AUTHORIZATION REQUEST FORM (JUNE 2022)

Pulmonary Arterial Hypertension

Member and Medication Information * indicates required field	
*Member ID:	*Member Name:
*DOB:	*Weight:
*Medication Name/Strength:	□ Do Not Substitute. Authorizations will be processed for the preferred Generic/Brand equivalent unless specified.
*Directions for use:	
Provider Information * indicates required field	
*Requesting Provider Name:	*NPI:
*Address:	
*Contact Person:	*Phone #:
*Fax #:	Email:
Medically Billed Information * indicates required field for all medically billed products	
*Diagnosis Code:	*HCPCS Code:
*Dosing Frequency:	*HCPCS Units per dose:
Servicing Provider Name:	NPI:
Servicing Provider Address:	
Facility/Clinic Name:	NPI:
Facility/Clinic Address:	
Fax form and relevant documentation including: laboratory results, chart notes and/or updated provider letter to Pharmacy PA at **855-828-4992,** to prevent processing delays.	

Select requested medication(s):

Preferred products are bold. *Non-Preferred Product Criteria also applies to (non-bolded) products.*

□ Adempas (riociguat) □ Adcirca (**tadalafil**) □ Alyq (**tadalafil**) □ Flolan (**epoprostenol**) □ **Letairis** (ambrisentan)
□ Opsumit (macitentan) □ Orenitram (treprostinil) □ Remodulin (treprostinil) □ Revatio (**sildenafil**) □ **Tracleer** (bosentan)
□ Tyvaso (treprostinil) □ Uptravi (selexipag) □ Veletri (**epoprostenol**) □ Ventavis (iloprost) □ Other: _____

Criteria for Approval: *(**All** criteria must be met)*

□ Medication prescribed by, or in consultation with a pulmonologist or cardiologist.

□ Diagnosis of pulmonary arterial hypertension, confirmed in adults by right heart catheterization.
Indicate mean PAP:_____

□ Patient had vasoreactivity testing and failed maximum tolerated doses of calcium channel blockers. Chart Note Page#:_____

□ Patient has WHO functional class of: □ II □ III □ IV

□ Indicate all of the following medications that the patient has tried and failed:

Nitric Oxide-cGMP Enhancers	Endothelin Receptor Antagonists	Prostacyclin Pathway Agonists	
□ Adcirca (**tadalafil**)	□ **Letairis** (ambrisentan)	□ Flolan (**epoprostenol**)	□ Uptravi (selexipag)
□ Adempas (riociguat)	□ Opsumit (macitentan)	□ Orenitram (treprostinil)	□ Veletri (epoprostenol)
□ Alyq (**tadalafil**)	□ **Tracleer** (bosentan)	□ Remodulin (treprostinil)	□ Ventavis (iloprost)
□ Revatio (**sildenafil**)		□ Tyvaso (treprostinil)	

Non-Preferred Product: *(Criteria above must also be met)*
□ Trial and failure of preferred product, per Utah Medicaid's PDL, or prescriber must demonstrate medical necessity for non-preferred product. Details: _____ Chart Note Page#:_____

NOTE:

- ❖ Per federal regulation, Medicaid does not reimburse for drugs used for the treatment of sexual dysfunction or erectile dysfunction. Pharmacies should dispense only those products with pulmonary hypertension NDCs.

Re-authorization Criteria:
Updated letter with medical justification or updated chart notes demonstrating positive clinical response with six-minute walk test or FEV_1.

Authorization:
28 days for titration dosing (up to three (3) months for Uptravi), or maintenance dosing = six (6) months

Re-authorization:
Up to six (6) months

PROVIDER CERTIFICATION
I hereby certify this treatment is indicated, necessary and meets the guidelines for use.

_____ _____
Prescriber's Signature Date

APPENDIX B: LITERATURE SEARCH STRATEGIES

Ovid Medline – Systematic Reviews

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 31, 2023>

1 pulmonary arterial hypertension/ 1961

2 PAH.ti,ab,kw,kf. 28429

3 (hypertension adj2 pulmonary).ti,ab,kw,kf. 54177

4 1 or 2 or 3 74032

5 pediatrics/ or infant/ or child/ or adolescent/ 3483218

6 (pediatric or paediatric).ti,ab,kw,kf. 406018

7 5 or 6 3588021

8 prostaglandins/ or endothelin receptor antagonists/ or phosphodiesterase 5 inhibitors/ 34676

9 (prostacyclin analogue* or (endothelin receptor adj3 (inhibit* or blocker*)) or phosphodiesterase type-5 inhibitor*).ti,ab,kw,kf. 2961

10 Epoprostenol/ or Iloprost/ or Bosentan/ or Sildenafil Citrate/ or Tadalafil/ 22556

11 (epoprostenol or Veletri or Flolan or iloprost or Ventavis or treprostinil or Remodulin or Tyvaso or Orenitram or ambrisentan or Letairis or bosentan or Tracleer or macitentan or Opsumit or sildenafil or Revatio or tadalafil or Alyq or Adcirca or Tadliq or selexipag or Uptravi or riociguat or Adempas).ti,ab,kw,kf. 15372

12 (drug$ or pharmacologic$ or pharmacother$ or medication$).ti. 582224

13 8 or 9 or 10 or 11 or 12 637173

14 4 and 7 and 13 915

15 meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. 501956

16 (MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt. 470078

17 15 or 16 584162

18 14 and 17 **35**

Ovid Medline – Randomized Controlled Trials

Prostacyclin analogs

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 07, 2023>

1 pulmonary arterial hypertension/ 1982

2 PAH.ti,ab,kw,kf. 28481

3 (hypertension adj2 pulmonary).ti,ab,kw,kf. 54298

4 1 or 2 or 3 74189

5 pediatrics/ or infant/ or child/ or adolescent/ 3485417

6 (pediatric or paediatric).ti,ab,kw,kf. 407422

7 5 or 6 3591004

8 Epoprostenol/ or Iloprost/ 14294

9 (epoprostenol or Veletri or Flolan or iloprost or Ventavis or treprostinil or Remodulin or Tyvaso or Orenitram).ti,ab,kw,kf. 4107

10 8 or 9 15558

11 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) 1386815

12 4 and 7 and 10 and 11 57

13 limit 12 to yr="2018 -Current" **7**

Ambrisentan

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to February 07, 2023>

1 pulmonary arterial hypertension/ 1982

2 PAH.ti,ab,kw,kf. 28481

3 (hypertension adj2 pulmonary).ti,ab,kw,kf. 54298

4 1 or 2 or 3 74189

5 pediatrics/ or infant/ or child/ or adolescent/ 3485417

6 (pediatric or paediatric).ti,ab,kw,kf. 407422

7 5 or 6 3591004

8 (ambrisentan or Letairis).ti,ab,kw,kf. 421

9 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) 1386815

10 4 and 7 and 8 and 9 **8**

Epistemonikos – Systematic Reviews

Date of search: February 6, 2023
Publication type filter: Systematic Review

(title:(("pulmonary arterial hypertension" OR PAH) AND (pediatric OR paediatric OR infant* OR newborn* OR neonate* OR child* OR adolescent*) AND (drug* OR pharmacologic* OR pharmacother* OR medication*)) OR title:(("pulmonary arterial hypertension" OR PAH) AND (pediatric OR paediatric OR infant* OR newborn* OR neonate* OR child* OR adolescent*) AND (epoprostenol OR Veletri OR Flolan OR iloprost OR Ventavis OR treprostinil OR Remodulin OR Tyvaso OR Orenitram OR ambrisentan OR Letairis OR bosentan OR Tracleer OR macitentan OR Opsumit OR sildenafil OR Revatio OR tadalafil OR Alyq OR Adcirca OR Tadliq OR selexipag OR Uptravi OR riociguat OR Adempas OR "prostacyclin analogue*" OR "endothelin receptor antagonist*" OR "endothelin receptor inhibitor*" OR "endothelin receptor blocker*" OR "phosphodiesterase 5 inhibitor*" OR "phosphodiesterase type-5 inhibitor*" OR "phosphodiesterase type 5 inhibitor*")) OR abstract:(("pulmonary arterial hypertension" OR PAH) AND (pediatric OR paediatric OR infant* OR newborn* OR neonate* OR child* OR adolescent*) AND (epoprostenol OR Veletri OR Flolan OR iloprost OR Ventavis OR treprostinil OR Remodulin OR Tyvaso OR Orenitram OR ambrisentan OR Letairis OR bosentan OR Tracleer OR macitentan OR Opsumit OR sildenafil OR Revatio OR tadalafil OR Alyq OR Adcirca OR Tadliq OR selexipag OR Uptravi OR riociguat OR Adempas OR "prostacyclin analogue*" OR "endothelin receptor antagonist*" OR "endothelin receptor inhibitor*" OR "endothelin receptor blocker*" OR "phosphodiesterase 5 inhibitor*" OR "phosphodiesterase type-5 inhibitor*" OR "phosphodiesterase type 5 inhibitor*")))

APPENDIX C: CLASSIFICATION OF PULMONARY HYPERTENSION

The classification of pulmonary hypertension (PH) in the pediatric population is identical to that for the adult population.[3] Notably, specific pediatric conditions and congenital diseases are included in the classification to enhance applicability to infants and children with PH.[3,5]

Table C1. Classification of Pediatric Pulmonary Hypertension, per ESC/ERS and WSPH[3,5,95]

Group	Pulmonary Hypertensive Conditions

Group 1: PAH	• Idiopathic PAH
	  ○ Vasoreactive non-responders
	  ○ Vasoreactive acute responders, also termed "PAH long-term responders to CCBs"[5]
	• Heritable PAH
	• Drug- and toxin-induced PAH
	• PAH associated with:
	  ○ Connective tissue disease
	  ○ Infections (ie, HIV, schistosomiasis)
	  ○ Portal hypertension
	  ○ CHD
	• PAH with overt features of venous/capillary involvement (PVOD/PCH)
	• PPHN syndrome[a]

Group 2: PH secondary to left heart disease	• Heart failure:
	  ○ With preserved ejection fraction
	  ○ With (mildly) reduced ejection fraction
	• Valvular heart disease
	• Congenital/acquired cardiovascular conditions resulting in post-capillary PH
	• Congenital post-capillary obstructive lesions
	  ○ Pulmonary vein stenosis
	  ▪ Isolated
	  ▪ Associated (prematurity, BPD)
	  ○ Coarctation of the aorta
	  ○ Cor triatriatum
	  ○ Obstructed total anomalous pulmonary venous return
	  ○ Mitral/aortic stenosis (including supra/subvalvular)

Group 3: PH secondary to lung diseases and/or hypoxia	• Obstructive lung disease or emphysema • Restrictive lung disease • Lung disease with mixed pattern of restrictive/obstructive • Hypoventilation syndromes • Hypoxia without lung disease (eg, high altitude) • Developmental lung disorders[b]

Table C1. Classification of Pediatric Pulmonary Hypertension, per ESC/ERS and WSPH[3,5,95]

Group	Pulmonary Hypertensive Conditions
Group 4: PH secondary to pulmonary artery obstructions	• CTEPH • Other pulmonary artery obstructions (eg, sarcomas, tumors [malignant or non-malignant], arteritis without connective tissue disease, hydatidosis, congenital pulmonary arterial stenoses)
Group 5: PH with mechanisms that are unclear, multifactorial, or both	• Hematological disorders (eg, chronic myeloproliferative disorders, inherited and acquired chronic hemolytic anemia) • Systemic disorders (eg, sarcoidosis, pulmonary Langerhans's cell histiocytosis, neurofibromatosis type 1) • Metabolic disorders (eg, Gaucher disease, glycogen storage diseases) • Chronic renal failure with or without hemodialysis • Pulmonary tumor thrombotic microangiopathy • Fibrosing mediastinitis • Complex CHD[c] ○ Segmental PH ▪ Isolated pulmonary artery of ductal origin ▪ Absent pulmonary artery ▪ Hemitruncus ▪ "Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries"[5] (page 6) ▪ Other ○ Single ventricle: unoperated, operated ○ Scimitar syndrome

[a] *PPHN can be idiopathic (15% to 20% of cases),[38] but it is described as a syndrome, and therefore, may be associated with the following disorders: down syndrome, meconium aspiration syndrome, myocardial dysfunction, structural cardiac diseases, hepatic and cerebral arteriovenous malformation, respiratory distress syndrome, transient tachypnea of the newborn, pneumonia/sepsis, developmental lung disease, perinatal stress, placental dysfunction (chorioamnionitis, pre-eclampsia, maternal hypertension), metabolic disease, or maternal smoking or drug use.[5]*

[b] *The following examples of developmental lung disorders are associated with pulmonary hypertension in pediatric patients: BPD, congenital diaphragmatic hernia, down syndrome, alveolar capillary dysplasia with "misalignment of veins" [FOXF1], surfactant protein abnormalities, pulmonary lymphangiectasia, lung hypoplasia, acinar dysplasia, pulmonary interstitial glycogenesis, TTF1/NKX2-1, TBX4, pulmonary alveolar proteinosis.*

[c] *"In these complex CHD categories…, the general definition of PH does not suffice and should be customised."[5] (page 7) Currently, additional studies are needed to determine if targeted agents are effective and safe in this patient population.*

Abbreviations: BPD, bronchopulmonary dysplasia; CCBs, calcium channel blockers; CHD, congenital heart disease; CTEPH, chronic thrombo-embolic pulmonary hypertension; ERS, European Respiratory Society; ESC, European Society of Cardiology; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; PVOD, pulmonary veno-occlusive disease; WSPH, World Symposium on Pulmonary Hypertension

APPENDIX D: SUPPLEMENTAL INFORMATION

The information contained in the tables below (**Tables D1, D2,** and **D3**) was also included in the Drug Utilization Review (DUR) report on PAH in adults, completed March 2023.

Mechanism of Action for PAH-specific Agents

Table D1 summarizes the mechanism of action for each agent, organized by drug class.

Table D1. Mechanism of Action for PAH-specific Agents, Organized by Drug Class[a]

Drug Class	Active Ingredient	Mechanism of Action per Product Labeling
Prostacyclin Analogs	Epoprostenol	Blocks platelet aggregation and directly vasodilates systemic and pulmonary arterial vasculature[14,15]
	Iloprost	Vasodilates systemic and pulmonary arterial vasculature and blocks platelet aggregation, but it is unclear how this latter effect impacts the treatment of PH[20]
	Treprostinil	Blocks platelet aggregation and directly vasodilates systemic and pulmonary arterial vasculature[16-19]
Endothelin Receptor Antagonists	Ambrisentan	Highly selective inhibitor of endothelin receptor subtype ET_A (binding affinity is >4000 fold greater than subtype ET_B receptors), resulting in vasodilation[12]
	Bosentan	A dual, competitive, endothelin receptor antagonist at ET_A and ET_B subtypes, with a modestly higher binding affinity for ET_A than ET_B[8]
	Macitentan	Blocks the binding of ET-1 to endothelin receptors (ET_A and ET_B), but the clinical influence of antagonizing dual receptor subtypes is unclear. Potentially helps to manage the upregulation of the ET system in patients with PAH to prevent organ damage and vascular hypertrophy[13]
Phosphodiesterase Type 5 Inhibitors	Sildenafil	Promotes vasodilation of the pulmonary vasculature by increasing the concentrations of cGMP within the pulmonary vascular smooth muscle by blocking PDE5, which is responsible for degrading cGMP[9-11,21]
	Tadalafil	
Prostacyclin Receptor Agonist	Selexipag	Selectively binds to the IP prostanoid receptor, promoting vasodilation, and thereby decreasing pulmonary vascular resistance and improving cardiac index. Although this agent inhibits platelet aggregation *in vitro*, it doesn't appear to effect platelet aggregation in healthy participants at standard dosages[96]
Soluble Guanylate Cyclase Stimulator	Riociguat	Stabilizes the binding of endogenous NO to sGC, and directly binds to sGC; both mechanisms increase cGMP production, thereby promoting vasodilation[90]

[a] *Information is reported based on package inserts (ie, prescribing information).*

Abbreviations: cGMP, cyclic guanosine monophosphate; ET, endothelin; NO, nitric oxide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; sGC, soluble guanylate cyclase

Table D2 summarizes the labeled contraindications, warnings, and precautions for PAH-specific agents.

Table D2. Labeled Warnings and Precautions for PAH-specific Agents[a]

Prostacyclin Analogs
Epoprostenol[14,15] • **Contraindications:** ○ Pulmonary edema while initiating dose; do not use if this happens (Veletri) ○ Congestive heart failure secondary to severe left ventricular systolic dysfunction ○ Hypersensitivity reaction to the active ingredient, excipients, or structurally related substances • **Warnings:** ○ Discontinue if pulmonary edema occurs during initiation, and do not retreat with this agent (Flolan) ○ Do not suddenly decrease the dose or discontinue the agent due to the risk of rebound PH, which has the potential to result in premature death ○ Starting the agent, and any dosing modifications require regular physiologic monitoring of the patient ○ For continuous, chronic use, an indwelling central venous catheter and anticoagulation (unless contraindicated) are recommended ○ Use may increase the risk of hemorrhagic complications, especially in patients predisposed to bleeding (Flolan)
Iloprost[20] • **Contraindications:** ○ None • **Warnings:** ○ Vital signs should be monitored during initiation due to the risk of hypotension and associated syncope; avoid use if systolic blood pressure is <85 mmHg ○ If pulmonary edema happens during use, discontinue immediately because this could be an indicator of pulmonary venous hypertension ○ Use may result in bronchospasm; severity or frequency may be greater in patients who have a history of hyperreactive airway disease
Treprostinil[16-19] • **Contraindications:** ○ Severe hepatic impairment (Orenitram) ○ None (Remodulin, Tyvaso DPI, Tyvaso) • **Warnings:** ○ Symptomatic hypotension, especially in patients with a lower systemic arterial pressure (Remodulin, Tyvaso DPI, Tyvaso) ○ Potential increased risk of bleeding (Remodulin, Tyvaso DPI, Tyvaso) ○ Use may result in bronchospasm; sensitivity may be greater in patients who have a history of hyperreactive airway disease (Tyvaso DPI, Tyvaso)

[a] *Information is reported based on package inserts (ie, prescribing information).*

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BCRP, Breast Cancer Resistance Protein; CTD, connective tissue disease; CYP, cytochrome P450; DPI, dry powder inhaler; ERA, endothelin receptor antagonist; GC, guanylate cyclase; NAION, non-arteritic anterior ischemic optic neuropathy; PAH, pulmonary arterial hypertension; PDE(5), phosphodiesterase (type 5); P-gp, P-glycoprotein; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; REMS, Risk Evaluation and Mitigation Strategy; sGC, soluble guanylate cyclase; ULN, upper limit of normal

Table D2. Labeled Warnings and Precautions for PAH-specific Agents[a]

- Dosage modifications may be required if CYP2C8 inducers or inhibitors are added or discontinued (Tyvaso DPI, Tyvaso)
- Do not suddenly decrease or stop the dose (or discontinue the agent [Orenitram]) because symptoms may become worse (Remodulin, Orenitram)
- If a continuous infusion is given, it is preferred to use subcutaneous delivery rather than an external infusion pump via an indwelling central venous catheter due to the increased risk of sepsis and blood stream infections, which can be life-threatening (Remodulin)
- Gradually titrate the dose in patients with hepatic insufficiency (Remodulin)
- Because the tablets are not dissolvable, the tablets can get lodged in the diverticulum in patients who have diverticulosis (Orenitram)

Prostacyclin Receptor Agonist

Selexipag[96]

- **Contraindications:**
  - Combination use with strong CYP2C8 inhibitors (eg, gemfibrozil)
  - Hypersensitivity reaction to the active ingredient, excipients, or any other constituent
- **Warnings:**
  - Underlying PVOD should be suspected if pulmonary edema or related signs occur during use; the agent should be discontinued if PVOD is confirmed

Endothelin Receptor Antagonists (ERAs)

Drug Class Warnings (Ambrisentan, Macitentan, and Bosentan, Unless Specified Otherwise)[8,12,13]

- **Contraindications:**
  - Black box warning: risk of embryo-fetal toxicity; use during pregnancy is contraindicated. Since these products have known embryo-fetal toxicity, a REMS program is set-up to ensure safe use in female patients of reproductive potential
  - Hypersensitivity reaction to the active ingredient, excipients, or any other constituent (Macitentan, Bosentan)
- **Warnings:**
  - Peripheral edema can result from ERA use, or as a consequence of PAH deterioration. A diuretic, fluid control, or in some severe cases, hospitalization for decompensated heart failure, or possible discontinuation of the causative agent may be required to help alleviate fluid retention
  - Underlying PVOD should be suspected if acute pulmonary edema or related signs occur during agent initiation; treatment with an ERA should be discontinued if PVOD is confirmed
  - ERA use may reduce sperm count; patients should be counseled on the possible impacts on fertility
  - Hematological changes, particularly reduction in hemoglobin and hematocrit concentrations, have occurred after receiving an ERA; avoid starting an ERA in patients with severe anemia. Hemoglobin should be measured at periodic intervals, which vary by agent:
    - Prior to initiation, one month after initiation, and occasionally thereafter as clinically indicated (Ambrisentan)

[a] *Information is reported based on package inserts (ie, prescribing information).*

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BCRP, Breast Cancer Resistance Protein; CTD, connective tissue disease; CYP, cytochrome P450; DPI, dry powder inhaler; ERA, endothelin receptor antagonist; GC, guanylate cyclase; NAION, non-arteritic anterior ischemic optic neuropathy; PAH, pulmonary arterial hypertension; PDE(5), phosphodiesterase (type 5); P-gp, P-glycoprotein; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; REMS, Risk Evaluation and Mitigation Strategy; sGC, soluble guanylate cyclase; ULN, upper limit of normal

Table D2. Labeled Warnings and Precautions for PAH-specific Agents[a]

- Prior to initiation and occasionally thereafter as clinically indicated (Macitentan)
- At one month and three months after initiation, and every 3 months thereafter (Bosentan)

Ambrisentan (Unique Contraindications/Warnings)[12]

- **Contraindications:**
  - Patients who have idiopathic pulmonary fibrosis, including those with PH (Group 3 PH)

Bosentan (Unique Contraindications/Warnings)[8]

- **Contraindications:**
  - Concomitant use of cyclosporine A or glyburide
- **Warnings:**
  - Black box warning: risk of hepatotoxicity, as indicated by increased liver enzymes (AST, ALT) >3 times the ULN and liver failure. Liver enzymes should be measured before initiating the agent and monthly thereafter; discontinue if elevated liver enzymes co-occur with signs of hepatic injury or dysfunction, or elevations in bilirubin ≥2 times the ULN

Macitentan (Unique Contraindications/Warnings)[13]

- **Warnings:**
  - Due to the risk of potential hepatotoxicity, liver enzymes (AST, ALT) should be measured before starting treatment, and repeated thereafter as clinically indicated; discontinue if clinically relevant increases in liver enzymes occur, or increases in liver enzymes coincide with elevations in bilirubin >2 times the ULN, or hepatotoxicity symptoms develop. For patients who do not develop hepatotoxicity symptoms, the agent can be re-started once liver enzyme levels have normalized

Phosphodiesterase Type 5 (PDE5) Inhibitors

Drug Class Warnings (Sildenafil and Tadalafil)[9-11,21]

- **Contraindications:**
  - Concomitant use with organic nitrates or GC stimulators including riociguat due to the possible potentiation of hypotensive effects
  - Hypersensitivity reaction to the active ingredient, excipients, or any other constituent
- **Warnings:**
  - Before prescribing the agent, consider whether the agent could have deleterious vasodilatory effects on patient's underlying cardiovascular condition(s) (eg, autonomic dysfunction, preexisting hypotension) or antihypertensive treatment (if applicable)
  - Avoid use in patients with PVOD, or with other PDE5 inhibitors (eg, Viagra, Cialis)
  - Sudden visual (NAION) or auditory impairment, including complete loss, have been reported with PDE5 inhibitor use; if this occurs, prompt medical care should be provided
  - Prolonged erections (>4 hours) and priapism (painful erections >6 hours) have been reported with PDE5 inhibitor use; if this occurs, patients should be advised to seek prompt medical emergency assistance. Risk of priapism is increased in patients with predisposing conditions (eg, multiple myeloma, sickle cell disease), or those with penile anatomical deformities (eg, cavernosal fibrosis)

[a] *Information is reported based on package inserts (ie, prescribing information).*

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BCRP, Breast Cancer Resistance Protein; CTD, connective tissue disease; CYP, cytochrome P450; DPI, dry powder inhaler; ERA, endothelin receptor antagonist; GC, guanylate cyclase; NAION, non-arteritic anterior ischemic optic neuropathy; PAH, pulmonary arterial hypertension; PDE(5), phosphodiesterase (type 5); P-gp, P-glycoprotein; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; REMS, Risk Evaluation and Mitigation Strategy; sGC, soluble guanylate cyclase; ULN, upper limit of normal

Table D2. Labeled Warnings and Precautions for PAH-specific Agents[a]

Sildenafil (Unique Contraindications/Warnings)[21]

- **Warnings:**
  - Avoid chronic use in pediatric patients due to the dose-dependent increased risk of mortality
  - Epistaxis has occurred in patients with PAH due to CTD (13%), and in those simultaneously taking an oral vitamin K antagonist (9%)
  - Serious vaso-occlusive crises, necessitating hospitalization, has been reported in patients with PH secondary to sickle cell disease; safety and effectiveness of this agent has not been determined for patients with PAH secondary to sickle cell anemia

Soluble Guanylate Cyclase Stimulator

Riociguat[90]

- **Contraindications:**
  - Black box warning: risk of fetal harm; use during pregnancy is contraindicated. Because of this risk, a REMS program is set-up to ensure safe use in female patients of reproductive potential
  - Concomitant use with any form of nitrates or nitric oxide donors (eg, amyl nitrite) due to the risk of hypotension
  - Combination use with either nonspecific or specific PDE inhibitors, or other sGC stimulators
  - Do not use in patients with PH secondary to idiopathic interstitial pneumonias
- **Warnings:**
  - Symptomatic hypotension or ischemia can potentially develop, especially in patients who have hypovolemia, hypotension at rest, autonomic dysfunction, severe obstruction of left ventricular outflow, or using strong CYP and P-gp/BCRP inhibitors, or antihypertensives; reducing the dose may be considered for patients who develop signs or symptoms of hypotension
  - Potential risk of serious bleeding, including hemorrhagic events
  - Underlying PVOD should be suspected if pulmonary edema or related signs occur during use; the agent should be discontinued if PVOD is confirmed

[a] *Information is reported based on package inserts (ie, prescribing information).*

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BCRP, Breast Cancer Resistance Protein; CTD, connective tissue disease; CYP, cytochrome P450; DPI, dry powder inhaler; ERA, endothelin receptor antagonist; GC, guanylate cyclase; NAION, non-arteritic anterior ischemic optic neuropathy; PAH, pulmonary arterial hypertension; PDE(5), phosphodiesterase (type 5); P-gp, P-glycoprotein; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; REMS, Risk Evaluation and Mitigation Strategy; sGC, soluble guanylate cyclase; ULN, upper limit of normal

Table D3 lists the drug-drug interactions for PAH-specific agents.

Table D3. Drug-drug Interactions for PAH-specific Agents[a]

Prostacyclin Analogs
Epoprostenol[14,15] • Blood pressure may decrease further when taken with antihypertensives, diuretics, or other vasodilators • Potential for increased risk of bleeding when taken concomitantly with anticoagulants or antiplatelets • Concentrations of digoxin may increase after starting epoprostenol, which could be clinically relevant in patients who are predisposed to digoxin toxicity (Veletri)
Iloprost[20] • Concomitant use of antihypertensives or vasodilators may potentiate hypotensive effects • Potential for increased risk of bleeding when taken concomitantly with anticoagulants or antiplatelets
Treprostinil[16-19] • Starting dose should be reduced to 0.125 mg BID when taken with a strong CYP2C8 inhibitor (eg, gemfibrozil); the dose should be adjusted every 3 to 4 days, not more often, in increments of 0.125 mg BID (Orenitram) • When taken with CYP2C8 inhibitors or inducers, dosage adjustments may be required (Remodulin)   ○ It is unclear whether CYP2C8 inhibitors or inducers produce a similar effect when taken with the inhaled formulations (Tyvaso, Tyvaso DPI)
Prostacyclin Receptor Agonist
Selexipag[96] • Contraindicated with combination use of *strong* CYP2C8 inhibitors • Dose should be reduced to once daily with concomitant use of a *moderate* CYP2C8 inhibitor (eg, clopidogrel) • Dose should be increased up to twice daily with combination use of an inducer of CYP2C8 and UGT 2B7 and 1A3 (eg, rifampin)
Endothelin Receptor Antagonists (ERAs)
Ambrisentan[12] • Ambrisentan dosage should be restricted to 5 mg once a day when taken in combination with cyclosporine
Bosentan[8] • Bosentan concentrations are increased when taken concomitantly with a CYP2C9 inhibitor (eg, amiodarone, fluconazole), or a strong CYP3A inhibitor (eg, itraconazole, ketoconazole), or moderate CYP3A inhibitor (eg, erythromycin, diltiazem); therefore it is recommended to avoid such combinations. Alternatively, drugs metabolized by CYP3A or CYP2C9 can be decreased when taken with bosentan because it is an inducer of these enzymes   ○ Contraindicated with combination use of cyclosporine A or glyburide • Reduces the effectiveness of hormonal contraception (oral, transdermal, implantable, transdermal); it is recommended to use additional other forms of contraception when taking bosentan

[a] *Information is reported based on package inserts (ie, prescribing information).*

Abbreviations: BCRP, Breast Cancer Resistance Protein; BID, twice daily; CYP, cytochrome P450; DPI, dry powder inhaler; PAH, pulmonary arterial hypertension; PDE(5), phosphodiesterase (type 5); P-gp, P-glycoprotein; sGC, soluble guanylate cyclase; TID, three times a day; UGT, uridine 5'-diphospho-glucuronosyltransferase

Table D3. Drug-drug Interactions for PAH-specific Agents[a]

Macitentan[13]

- Avoid combination use of CYP3A4 inducers or inhibitors, and moderate dual CYP3A4 and CYP2C9 inhibitors, or combination use of *both* a moderate CYP2C9 and CYP3A4 inhibitor

Phosphodiesterase Type 5 (PDE5) Inhibitors

Sildenafil[21]

- Contraindicated when used in combination with nitrates
- Concomitant use of amlodipine or alpha-blockers may potentiate hypotensive effects; blood pressure should be monitored in patients taking both an antihypertensive and sildenafil
- Avoid use with ritonavir and other potent CYP3A inhibitors, and other PDE5 inhibitors (eg, Viagra)

Tadalafil[9-11]

- Contraindicated to use nitrates within 48 hours of tadalafil
- Concomitant use of alpha-blockers may potentiate hypotensive effects
  - Combination use with antihypertensives (eg, amlodipine, enalapril, metoprolol) may result in minor reductions in blood pressure
- Risk of experiencing orthostatic signs and symptoms is increased with concomitant alcohol consumption (eg, ≥5 units)
- Tadalafil should be discontinued at least 24 hours before initiating ritonavir, and can be re-started at least one week after starting ritonavir
- Avoid use with potent CYP3A inhibitors and inducers

Soluble Guanylate Cyclase Stimulator

Riociguat[90]

- Contraindicated to use with other sGC stimulators, nitrates or nitric oxide donors, or PDE inhibitors
  - Avoid taking riociguat within 24 hours of sildenafil
  - Avoid taking riociguat "24 hours before or within 48 hours after tadalafil"[90] (page 6)
- Combination use with strong CYP and P-gp/BCRP inhibitors (eg, itraconazole, ritonavir) increase the concentrations of riociguat; consider starting at a lower dose of 0.5 mg TID. Patients should be monitored for symptoms or signs of hypotension
- Strong CYP3A inducers (eg, phenytoin, carbamazepine, St. John's Wort) can decrease concentrations of riociguat, but dosing recommendations are not provided for concomitant use
- Higher dosages may be needed in patients who are active smokers
- Administration of antacids (eg, aluminum hydroxide) should be separated by at least 1 hour

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Abbreviations: BCRP, Breast Cancer Resistance Protein; BID, twice daily; CYP, cytochrome P450; DPI, dry powder inhaler; PAH, pulmonary arterial hypertension; PDE(5), phosphodiesterase (type 5); P-gp, P-glycoprotein; sGC, soluble guanylate cyclase; TID, three times a day; UGT, uridine 5'-diphospho-glucuronosyltransferase

Pharmacology of PAH-specific Agents

Prostacyclin Pathway — Endogenous prostacyclin promotes vasodilation in the pulmonary vascular smooth muscle, and has other effects including antiproliferation and antithrombosis.[4,6] Patients with PAH have decreased levels of prostacyclin.[4,6] Prostacyclin analogs (eg, **epoprostenol, iloprost, treprostinil**) inhibit platelet aggregation and vasodilate systemic and pulmonary arterial vasculature.[14-20]

Endothelin Pathway — Plasma and pulmonary concentrations of endothelin-1 (ET-1), a potent vasoconstrictor, are increased in patients with PAH.[8,12] ET-1 and its associated receptors (ET_A and ET_B) facilitate vasoconstriction, proliferation, fibrosis, inflammation, and hypertrophy.[13] ERAs (eg, **ambrisentan, bosentan, macitentan**) block the binding of ET-1 to ET_A and ET_B receptor subtypes, with varying degrees of affinity (depending on the agent).[8,12,13]

Phosphodiesterase Type 5 Pathway — In patients with PAH, the PDE5 enzyme responsible for degrading the vasodilator, cyclic guanosine monophosphate (cGMP), is upregulated; this results in an inflated vasoconstrictive state.[4] Furthermore, the release of nitric oxide is impaired in patients with PAH, causing decreased concentrations of cGMP in the pulmonary vascular smooth muscle.[9] PDE5 inhibitors (eg, **sildenafil, tadalafil**) block the breakdown of cGMP, thereby increasing the concentrations of cGMP within the pulmonary vascular smooth muscle, promoting vasodilation.[9-11,21]