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Drug Class Update: Pulmonary Hypertension

Date of Review: October 2021

Date of Last Review: September 2018
Dates of Literature Search: 01/01/2018 - 06/30/2021

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Pulmonary hypertension (PH) is classified into 5 specific types. Historically, pulmonary arterial hypertension (PAH; World Health Organization [WHO] group 1) and chronic thromboembolic pulmonary hypertension (CTEPH; WHO group 4) are the only types of PH which have been treated with targeted drug therapies. This review evaluates new comparative evidence published since the last review as well as new evidence for nebulized treprostinil which recently received an expanded indication for pulmonary hypertension associated with interstitial lung disease. It is the first targeted therapy FDA-approved for pulmonary hypertension due to lung disease (WHO group 3).

Research Questions:
1. Are there differences in efficacy or effectiveness of initial monotherapy, initial combination therapy, or sequential combination therapy (i.e., add-on therapy) for treatment of PH based on stage of the disease for clinical outcomes such as exercise capacity, lung function, disease progression, hospitalizations, or mortality?
2. Are there differences in the safety profiles of initial monotherapy, initial combination therapy, or sequential combination therapy (i.e., add-on therapy) for treatment of PH?
3. Are there specific subpopulations based on disease severity (e.g., symptom severity or World Health Organization [WHO] functional class) or patient characteristics (e.g., ethnicity, race, comorbidities) that may benefit more from a specific drug or combination of drugs?

Conclusions:
- Evidence remains insufficient for use of targeted therapies in pulmonary hypertension due to left heart disease (WHO group 2).[1]
- There is low quality evidence from a single randomized controlled trial (RCT) that use of inhaled treprostinil four times daily has a modest benefit on exercise capacity in patients with pulmonary hypertension due to interstitial lung disease (WHO group 3) with no difference in mortality, hospitalizations due to pulmonary hypertension, or quality of life.[2] The average 6-minute walk distance (6MWD) improved by 21 meters compared to a decline of 10 meters with placebo (mean difference [MD] 31.12 m; 95% confidence interval [CI] 16.85 to 45.39).[2] Minimum clinically important differences (MCID) referenced in the literature for PAH and interstitial lung disease range from 21 to 45 meters.[2,3]

- Few trials directly compare treatments in pulmonary arterial hypertension (WHO group 1). Sildenafil may increase exercise capacity as evaluated by the 6MWD when compared to bosentan (MD 55m, 95% CI 0.1 to 109.9), but a trial evaluating ambrisentan compared to tadalafil found no difference in the 6MWD between groups (27m vs. 22.7m).[4] Similarly, improvement in WHO functional class or deterioration of functional class was not different upon comparison of ambrisentan and tadalafil.[4] Intravenous (IV) prostanoid therapy may have a larger treatment effect on exercise capacity, functional status, and mortality compared to other routes of administration in patients with PAH, but more direct comparisons are needed.[3] No studies have been powered to determine differences in mortality and most trials have evaluated only short-term treatment.
- In PAH (WHO group 1), combination therapy with a PDE-5 inhibitor may have slight improvements in 6MWD and quality of life compared to monotherapy, but differences are small and failed to meet thresholds of clinical significance.[5] There was no difference WHO functional status improvement or mortality with use of PDE-5 inhibitor vs. placebo (on combination therapy) based on moderate quality evidence.[5]

Recommendations:
- Update prior authorization criteria to include expanded indications.
- No PDL changes recommended based on current evidence.
- No changes were made to PDL after evaluation of costs in executive session.

Summary of Prior Reviews and Current Policy:
There is limited direct comparative evidence evaluating efficacy and safety of treatments for PAH. The majority of available RCTs are placebo-controlled and evaluate changes in functional status or exercise capacity using the 6MWD. Most studies have not been powered to determine differences in morbidity or mortality. Prior reviews suggest that there are no statistically significant differences in clinical worsening (defined as change in WHO functional class, initiation of treatment with intravenous or subcutaneous prostanoids, all-cause mortality, heart or lung transplant, or atrial septostomy) between monotherapy treatments for treatment-naïve patients with PAH and WHO functional class II or III.[6] Pooled data based on drug class has suggested that oral phosphodiesterase(PDE)-5 inhibitors and intravenous epoprostenol may be associated with a statistically significant mortality reduction compared to placebo.[3] Sequential (add-on) combination therapy may be considered to slow clinical worsening compared to monotherapy. However, there is little data to guide the duration of initial drug therapy before switching or adding another drug.[6] Oral and inhalation therapies have been considered an appropriate option for class II-IV patients but do not necessarily negate the need for injectable prostanoids. Preferred oral formulations include bosentan and sildenafil. Historically, intravenous epoprostenol had been the treatment of choice in class IV patients based on recommendations from the American College of Chest Physicians and the American College of Cardiology Foundation/American Heart Association and is currently the preferred intravenous formulation.[6,7]

A PA is currently required for sildenafil to ensure it is used for a funded condition, and clinical PA criteria is required for all non-preferred products listed in **Appendix 1**. Non-preferred products must be prescribed by a pulmonologist or cardiologist. In patients with pulmonary artery hypertension (WHO Group 1), oral therapy may be considered for patients with functional class II-IV symptoms. Riociguat may also be approved for patients with chronic thromboembolic pulmonary hypertension (WHO Group 4) and functional class II-IV symptoms. Intravenous therapy may be approved for patients with pulmonary arterial hypertension (WHO Group 1) and functional class III-IV symptoms.

Background:
Pulmonary hypertension (PH) is defined as a rise in mean pulmonary arterial pressure to greater than 20 mmHg at rest.[8] PH is classified into 5 groups: pulmonary arterial hypertension (PAH; WHO group 1), PH due to left heart disease (WHO group 2), PH due to lung disease and hypoxia (WHO group 3), chronic thromboembolic pulmonary hypertension (CTEPH, WHO group 4) and PH with an unclear multifactorial cause (WHO group 5).[8] Each type of PH has a unique

etiology, pathology and management strategy. Historically, PAH and CTEPH are the only types of PH with specific targeted drug therapies, and nebulized treprostinil recently received FDA approval for PH due to lung disease (WHO group 3). Etiology for PAH and CTEPH often includes multiple mechanisms including abnormal function or expression of potassium channels in smooth muscle and abnormal nitric oxide production causing vasoconstriction, endothelial dysfunction, and thrombosis. Hemodynamic changes and vascular remodeling eventually lead to long-term complications such as right ventricular dysfunction, arrhythmias, and ascites. The estimated incidence of adults with PAH is approximately 15-60 cases per 1 million adults.[9] The exact incidence of CTEPH in the US is unclear.[10] In the Oregon Health Plan (OHP) fee-for-service (FFS) population, approximately 1050 patient had at least one claim indicating a diagnosis of unspecified pulmonary hypertension in 2020. Over the last quarter in 2021, there were approximately 40 OHP FFS patients with claims for targeted PH medications with the majority of use for PDE-5 inhibitors.

Functional status for patients with PH often relies on WHO classes which categorize symptom severity into the following 4 categories: no limitations in physical activity (class I), slight limitations in physical activity (class II), marked limitations in physical activity (class III), and symptoms at rest (class IV).[8] Symptoms primarily include respiratory dyspnea, syncope, chest pain, exercise intolerance, and peripheral edema. The estimated 3-year survival is 58 to 73% with worsening prognosis for patients with higher functional class, rapidly progressive disease, need for prostanoid therapy, or recurrent hospitalizations.[11] Increased disease severity, impaired exercise capacity, and risk for clinical morbidity or mortality outcomes may also be evaluated using a variety of hemodynamic factors including cardiac index, the 6MWD , oxygen saturation, and right arterial pressure.[9,12]

Current standard of care for patients with PAH (WHO group 1) includes oral calcium channel blockers for patients who respond to acute vasoreactive testing (approximately 10% of patients), diuretics for fluid retention, digoxin to improve cardiac output and slow ventricular rate, and anticoagulants to decrease risk for thromboembolic events.[9] Other supportive care includes oxygen, supervised physical activity, and rehabilitation.[9] PAH-specific therapies may also be considered for patients with functional class II-IV symptoms. Current PAH-specific treatment options include the following drugs:
- PDE-5 inhibitors: sildenafil and tadalafil
- Endothelial receptor antagonists (ERAs): bosentan, macitentan, and ambrisentan
- soluble guanylate cyclase stimulators: riociguat
- prostacyclin receptor agonists: selexipag
- prostanoids: epoprostenol (intravenous), treprostinil (inhaled, oral, subcutaneous, intravenous), and iloprost (inhaled)

In patients with CTEPH (WHO Group 4), standards of care include supervised cardiopulmonary exercise rehabilitation, supplemental oxygen, diuretics for fluid retention, and lifetime anticoagulants to prevent thromboembolic events. Pulmonary endarterectomy is recommended for surgery-eligible patients, and if successful, may potentially be curative with survival rates of 74 to 89% at 5 years after surgery.[9,10] However, not all patients are eligible for surgery, and the disease either recurs or is refractory to surgery in 5 to 35% of cases.[11] Patients who are not surgical candidates may consider drug therapy, primarily treatment with riociguat to improve exercise intolerance. Riociguat is currently the only PAH-specific therapy also FDA-approved for patients with CTEPH. Current guidelines suggest PAH therapies may be considered for off-label use in patients with inoperable CTEPH.[10] However, recommendations are supported by limited evidence such as small RCTs, non-randomized studies, indirect evidence, or lack of clinical outcome data.[10]

To date, targeted therapies have not been recommended in patients with PH due to lung diseases or hypoxia (WHO group 3). The most common etiologies include chronic obstructive pulmonary disease (COPD) in 50-90% of patients and interstitial lung disease in up to 40% of patients.[8] Current guidelines recommend treatment of the underlying lung condition and do not recommend targeted therapies for PH.[8] This recommendation is based on limited evidence indicating that targeted therapies including (iloprost, riociguat, and ambrisentan) may not improve symptoms or functional outcomes, and in the case of

riociguat and ambrisentan, may be associated with increased risk of adverse events including mortality.[8] Because of this risk, riociguat and ambrisentan are contraindicated in patients with interstitial lung disease.[8] However, nebulized treprostinil recently received FDA-approval to improve exercise capacity in patients with PH associated with interstitial lung disease based on results from a single phase 3 RCT.[2] Treatment effects were generally modest, and there was no difference observed in mortality, quality of life, or hospitalizations due to PH.[2]

Goals of therapy for all types of pulmonary hypertension include morbidity and mortality reduction, symptom improvement, and decreased disease progression. Outcomes studied in clinical trials include hemodynamic endpoints, 6MWD, and time to clinical worsening endpoints. The majority of trials have not been designed to evaluate long-term outcomes of mortality or disease progression. 6MWD is often used to evaluate exercise capacity. While worse 6MWD at baseline and rapid decline in 6MWD (>15% over 1 year) may have some prognostic value, improvements of up to 15% change in 6MWD over 1 year have not demonstrated any correlation with mortality reduction or disease progression for patients with PAH.[13] Patients with 6MWD greater than 440 to 500 meters are generally considered to be at low risk for clinical events,[9,12] and minimum clinically important differences referenced in the literature range from 21 to 45 m depending on the type and cause of the pulmonary disease.[2,3] Many other scales can be used to evaluate symptom improvement. Common scales which evaluate respiratory symptoms include the Borg dyspnea scale which evaluates dyspnea symptoms on a 0-7 point scale (MCID 1 point)[5] and the St George's Respiratory Questionnaire which evaluates quality of life on a 0-100 point scale (MCID 4 points). Often clinical worsening is defined as a composite endpoint which may include a variety of outcomes including change in WHO functional class, initiation of treatment with IV or SC prostanoids, hospitalization, all-cause mortality, heart or lung transplant, or atrial septostomy.[14]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A series of Cochrane systematic reviews were published in 2019 which evaluated drug therapy for pulmonary hypertension. Drug therapies included PDE-5 inhibitors,[5] prostacyclin,[3] and ERAs.[4]

A Cochrane review evaluated efficacy and safety of PDE-5 inhibitors identified evidence from 19 trials in patients with pulmonary arterial hypertension (WHO group 1), 5 trials in patients with left heart disease (WHO group 2), 5 trials in patients with PH secondary to lung disease (WHO group 3) and 3 trials in chronic thromboembolic disease (WHO group 4). Most trials included participants with WHO functional class II or III symptoms and subgroups based on functional class demonstrated similar magnitude of benefit.[5] For use in PAH (WHO group 1), PDE-5 inhibitors demonstrated statistical improvement in the following outcomes: Monotherapy PDE-5 inhibitor compared to placebo:[5]
- 6MWD: MD 48 m (95% CI 40 to 56); moderate quality evidence with significant heterogeneity (I^2=71%); baseline risk with placebo of 170 to 319 meters

- Improvement in WHO functional class: 61 vs. 358 events per 1000 people; odds ratio (OR) 8.59 (95% CI 3.95 to 18.72); high quality evidence
- Mortality: 41 vs. 9 events per 1000 people; OR 0.22 (95% CI 0.01 to 0.68); high quality evidence
- Quality of life was evaluated in 2 RCTs (n=163). Evidence was mixed with significant heterogeneity between trials.
- Clinical worsening requiring hospitalization

PDE-5 inhibitor compared to placebo (on combination therapy):[5]
- 6MWD: MD 20 m (95% CI 9 to 30); moderate quality evidence; baseline risk with placebo of 341 to 377 meters; results did not meet the MCID of 41 meters
- Quality of life (SF-36; scale range 1 to 100; MCID 13 for physical domain and 15 for vitality domain): improvement of 0.3 points (95% CI 4.7 to 4.1) with placebo compared to 7.8 points (95% CI 3.6 to 12.1) with sildenafil; moderate quality evidence
- There was no statistical difference in WHO functional class or mortality for combination therapy; moderate quality evidence

PDE-5 inhibitor compared to ERA:[5]
- 6MWD: MD 49 (95% CI 4 to 95); 2 RCTs (n=36); low quality evidence; baseline risk with ERA of 290 to 354 meters
- Quality of life (Kansas City Cardiomyopathy quality-of-life questionnaire; 23 items): MD 22 (95% CI 9 to 35); 1 RCT (n=25); low quality evidence
- There was no statistical difference in WHO functional class or mortality; moderate quality evidence

In patients with PH due to left heart disease (WHO group 2), 5 RCTs compared PDE-5 inhibitors to placebo, with statistical benefit in WHO functional class, 6MWD, and quality of life based on moderate quality evidence. Treatment duration ranged from 12 weeks to 12 months.[5] Differences in the 6MWD were modest (MD 34 m; 95% CI 23 to 46) and change in WHO functional class occurred on average in 403 patients per 1000 with placebo compared to 263 patients per 1000 with PDE-5 inhibitors (OR 0.53; 95% CI 0.32 to 0.87).[5] There was no difference in mortality based on moderate quality evidence.

In patients with PH due to lung disease (WHO group 3), PDE-5 inhibitors were associated with statistical improvement in WHO functional class (50 vs. 700 per 1000 people; OR 44.33; 95% CI 4.78 to 410.94; 1 RCT; n=40; low quality evidence) and 6MWD (27 m; 95% CI 2 to 51; 5 RCTs; n=350; high quality evidence) over 12 to 16 weeks.[5] However, only one small study evaluated WHO Functional class improvements, and magnitude of benefit for changes in 6MWD was small. No statistical benefit was observed for quality of life (moderate quality evidence) and no studies evaluated mortality.[5]

Three RCTs evaluated patients with CTEPH (WHO group 4). PDE-5 inhibitors had no difference compared to placebo in 6MWD, improvement in WHO functional class, or quality of life based on low quality evidence.[5] Compared to bosentan, there was no statistical difference in 6MWD (moderate quality evidence) or mortality (low quality evidence).[5]

Evidence for use of prostacyclin in pulmonary arterial hypertension (WHO group 1) included 17 trials (n=3765) of intravenous, subcutaneous, oral and inhaled prostanoids or prostacyclin receptor agonists.[3] The majority of trials included patients with functional class III symptoms (range class II to IV). Compared to placebo or usual care, use of prostacyclin had a modest improvement for clinical outcomes over a mean follow-up time of 15 to 17 weeks:[3]
- WHO functional class: OR 2.39; 95% CI 1.72 to 3.32; 116 vs. 239 events per 1000 patients; moderate quality evidence
- 6MWD: MD 19.5m; 95% CI 14.82 to 24.19; low quality evidence
- dyspnea symptoms: standardized mean difference (SMD) 0.21; 95% CI 0.11 to 0.32; low quality evidence
- mortality: OR 0.60; 95% CI 0.38 to 0.94; 39 vs. 24 events per 1000 patients; moderate quality evidence
- quality of life: SMD 0.28; 95% CI 0.04 to 0.42; moderate quality evidence

However, overall differences from placebo were small, and the average change in the 6MWD and Borg dyspnea score did not meet minimum clinically important differences referenced in the literature (MCID of 41 m or 1 point, respectively).[3] Subgroup analyses demonstrated improvements in 6MWD, WHO functional class, and mortality were largest for intravenous therapies compared to subcutaneous or oral routes of administration.[3] Upon comparison of selexipag to placebo there were small but not clinically significant improvements in 6MWD (MD 12m; 95% CI 1.9 to 23.3; high quality evidence) with no statistical difference observed in WHO functional class, dyspnea scores or mortality over a mean follow-up period of 17 to 40 weeks based on moderate quality evidence.[3] Adverse events occurring more commonly with treatment included vasodilation, headache, jaw pain, diarrhea, nausea or vomiting, extremity pain, myalgia, upper respiratory tract events, and infusion site reactions. For intravenous therapy, there was a 12 to 25% increased risk of serious non-fatal events related to administration including sepsis, hemorrhage, pneumothorax and pulmonary embolism.[3]

Evidence for ERAs included 17 RCTs (n=3322) evaluating therapy over 12 to 24 weeks compared to placebo or PDE-5 inhibitors for PAH (WHO group 1).[4] Compared to placebo there was moderate evidence that ERAs improved 6MWD (MD 25.06m; 95% CI 17.13 to 32.99; I^2=34%), proportion of patients with improved functional class (230 vs. 175 per 1000 patients; OR 1.41; 95% CI 1.16 to 1.70), and odds of functional class deterioration (OR 0.43; 95% CI 0.26 to 0.72; I^2=40%).[4] There was low quality evidence of no clinical or statistical difference in the Borg dyspnea index compared to placebo over an average treatment duration of 30 weeks (MD -0.43 units, 95% CI -0.90 to 0.04; MCID of 1 unit).[4] There was no statistical difference in mortality compared to placebo (OR 0.78, 95% CI 0.58 to 1.07; low quality evidence).[4] Data for risk of hepatic toxicity over a mean duration of 25 weeks did not achieve statistical significance, though the direction of effect favored placebo (37 vs. 67 per 1000 patients; OR 1.88; 95% CI 0.91 to 3.90).[4] Subgroup analyses evaluating selective and non-selective endothelin receptor antagonists demonstrated no differences between groups for all clinical outcomes.[4] Two trials evaluated ambrisentan or bosentan compared to PDE-5 inhibitors. Sildenafil may increase exercise capacity as evaluated by the 6MWD when compared to bosentan (MD 55m, 95% CI 0.1 to 109.9), but a trial evaluating ambrisentan compared to tadalafil found no difference in the 6MWD between groups (27m vs. 22.7m).[4] Similarly, improvement in WHO functional class or deterioration of functional class was not different upon comparison of ambrisentan and tadalafil.[4]

A high quality systematic review assessed efficacy and safety of targeted drug therapies for use in PH due to left heart failure; trials included left heart failure with either reduced or preserved ejection fraction.[1] The primary outcome of the study assessed exercise capacity, and secondary clinical outcomes included mortality, hospitalization, and treatment discontinuations. Twenty-two studies (n=5448) were included in the analysis.[1] Only 3 trials were rated with low risk of bias; most studies had high (n=8) or unclear (n=11) risk of bias which significantly limits confidence in the treatment effects.[1] Duration of trials ranged from 12 to 52 weeks (median: 22 weeks).[1] Fifteen trials evaluated the impact of PDE-5 inhibitors, ERAs, prostanoids, and soluble guanylate cyclase stimulators on exercise capacity. Overall these therapies were associated with a statistically significant improvement in exercise capacity (SMD 0.29, 95% CI 0.08 to 0.50, p=0.006) with significant heterogeneity between studies (I^2=72%).[1] Pre-specified sensitivity analyses identified that study duration and outcome used for assessment of exercise capacity (particularly use of VO_2 peak) contributed to heterogeneity.[1] Additionally subgroup analysis indicated that results were influenced by patients with use of PDE-5 inhibitors or prostanoids, and patients with heart failure with reduced ejection fraction (HFrEF) who had had improvements in exercise capacity.[1] Upon analysis of secondary outcomes, there was an increased risk of treatment discontinuation compared to standard of care (17.4% vs. 14.6%; relative risk [RR] 1.31; 95% CI 1.15 to 1.50; p<0.001).[1] Authors found no overall difference in mortality or hospitalizations upon analysis of all included trials.[1] However, pre-specified sensitivity analyses identified increased risk of all-cause mortality compared to standard of care upon exclusion of one trial evaluating bosentan use (RR 1.26; 95% CI 1.04 to 1.53; p=0.02, I2=0%).[1] Of note, while this trial did not identify an increased mortality risk, bosentan was associated with an increased risk of hospitalization associated with worsening in heart failure. Overall, authors conclude that increased risk of mortality could not be ruled out.[1] Results for all outcomes were similar upon exclusion of trials with high risk of bias (though all studies evaluating prostanoids had high risk).[1] Authors noted several other limitations of the analysis including lack of reporting for standard heart failure therapy, inadequate documentation of severity or presence of PH associated with heart failure, variability in scales used to assess exercise capacity, and lack of correlation between exercise capacity and more objective clinical

outcomes such as hospitalization and mortality.[1] Targeted therapies for PH were associated with only modest improvements in exercise capacity, was associated with an increased rate of treatment discontinuation (number needed to harm [NNH] of 35), and may be associated with an increased risk of death.[1] Overall, based on these limitations, authors concluded that evidence remains insufficient for use of targeted therapies in patients with pulmonary hypertension associated with left heart disease.[1]

After review, 15 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria),[15-24] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[17,25-28] setting (e.g., inpatient),[29] or outcome studied (e.g., non-clinical).

New Guidelines:
No new high quality guidelines were identified.

New Formulations or Indications:
In October 2019, oral, extended-release treprostinil tablets received an expanded FDA-approved indication to delay disease progression in patients with PAH (WHO group 1). Treprostinil was previously indicated to increase exercise capacity in this population. Impact on disease progression was evaluated in a multicenter, double-blind, placebo-controlled trial enrolling 690 patients.[30] Disease progression was defined as the first clinical morbidity or mortality event. Treprostinil was evaluated as add-on therapy to a PDE-5 inhibitor or soluble guanylate cyclase stimulator (72%), or as add-on therapy to an ERA (28%).[30] At baseline, patients had an average 6MWD of 396 meters with 63% categorized as WHO functional class II indicating only slight limitations in physical activity.[30] The primary study outcome was a composite time to the first clinical worsening event and included death, hospitalization due to PAH, disease progression, initiation of prostacyclin treatment, or unsatisfactory long-term clinical response. Patients randomized to treprostinil had a decreased time to event rate compared to placebo (26% vs. 36%; hazard ratio [HR] 0.75; 95% CI; 0.57, 0.99; p=0.039) which was primarily driven by difference between groups in disease progression (14.5% vs. 5.5%).[30] Disease progression was defined as a 15% decline in 6MWD plus an increase in either WHO Functional Class or worsening of signs or symptoms of right heart failure.[30] There was no difference in mortality or hospitalizations or initiation of prostacyclin treatment.[30] The median time to the first event was 46 weeks in patients treated with treprostinil compared to 37 weeks with placebo (median difference of 9 weeks).[30] Despite adequate randomization methods, evidence was limited by differences between groups in baseline risk (with treprostinil patients having a higher risk of disease progression) and significantly higher attrition rate in the treatment group compared to placebo (30.9% vs. 16.3%).[30] Study discontinuation due to adverse events occurred with 18.8% of patients receiving treprostinil compared to 4.1% with placebo (NNH 6; HR 4.62; 95% CI 2.59 to 8.23; p<0.001).[30]

In March 2021, treprostinil nebulized inhalation received an expanded indication to improve exercise capacity in patients with PH associated with interstitial lung disease (WHO group 3). FDA approval was based on a phase 3, double-blind, randomized, placebo-controlled trial evaluating use of nebulized treprostinil four times daily to placebo (n=326).[2] Patients included in the trial had group 3 pulmonary hypertension confirmed by right heart catheterization, evidence of lung disease confirmed by chest CT scan, and ability to walk at least 100 meters during the 6 minute walk test.[2] Patients could not receive concomitant therapy for pulmonary hypertension, and when applicable, treatment for interstitial lung disease was required to be stable during the trial. Though methods used to randomize patients were adequate, there were slight variations in baseline characteristics between groups based on age (mean 65.6 vs. 67.4 years with placebo), ethnicity (white patients 69% vs. 77% with placebo), and 6MWD (254 vs. 265 meters with placebo).[2] Patients randomized to treprostinil were also more likely to have lung disorders associated with connective tissue disease (24% vs. 20%) and less likely to have lung disease associated with idiopathic interstitial pneumonia (40% vs. 50%).[2] It is currently unclear how these differences may impact results. The primary outcome was change in the 6MWD at 16 weeks, and treprostinil demonstrated a modest clinical improvement over placebo (21 m vs. -10 m; MD 31.12 m; 95% CI 16.85 to 45.39).[2] An important clinical

secondary endpoint included clinical worsening defined as hospitalization for a cardiopulmonary indication, 15% decrease in 6MWD from baseline at 2 consecutive visits, lung transplantation, or death. More patients treated with placebo experienced a clinical worsening event (33.1% vs. 22.7%; HR 0.61; 95% CI 0.40 to 0.92) with largest differences driven by patients with a 15% decline in 6MWD (16% vs. 8%) or hospitalization (14.7% vs. 11%; p=0.41).[2] Quality of life was also evaluated using the St. George's Respiratory Questionnaire with no difference between groups.[2] A significant proportion of patients (23-24%) discontinued treatment early over the 16-week treatment period which increases risk of attrition bias.[2] Discontinuations due to adverse events occurred in 10% of patients randomized to treprostinil and 8% of patients receiving placebo.[2] The most common adverse events occurring more commonly than placebo included cough, headache, dizziness, diarrhea, throat irritation and oropharyngeal pain.[2]

In July 2021, a new formulation of intravenous selexipag was FDA-approved for PAH (WHO group 1).[31] Oral selexipag tablets were previously approved for this population. Injectable therapy should be administered as an 80 minute infusion twice daily and is indicated for patients who are temporarily unable to take oral therapy.[31]

New FDA Safety Alerts:
Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Iloprost[32]	Ventavis®	12/2019	Warnings and Precautions	Avoid contact with skin and eyes and ingestion. Ventavis® solution should not be allowed to come into contact with the skin or eyes; ingestion of Ventavis solution should be avoided.
Tadalafil[33]	Adcirca®	9/2020	Contraindications	Labeling was updated to emphasize risk of drug interactions with concomitant organic nitrates with tadalafil. Use of nitrates within 48 hours of the last dose of tadalafil is not recommended.

Randomized Controlled Trials:
A total of 107 citations were manually reviewed from the initial literature search. After further review, 104 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results/Conclusions
Hoeper, et al. REPLACE[34] OL, MC, switching, RCT 24 weeks N=226	1. Remain on a PDE-5 inhibitor (sildenafil ≥60mg/day or tadalafil 20-40mg/day) 2. Switch to riociguat 2-5 mg TID	symptomatic PAH at intermediate risk of 1-year mortality	Clinical improvement at 24 weeks defined as absence of clinical decline AND improvement in at least 2 variables including 6MWD, WHO functional status, or NT-proBNP	1. 23 (20%) 2. 45 (41%) OR 2.78 (95% CI 1.53 to 5.06) p=0.0007 *In patients with symptoms on current PDE-5 inhibitor therapy, switching therapy resulted in functional improvement in an open-label trial.*

McLaughlin, et al. AMBITION[35]
 	
Prespecified subgroup analysis of a DB, MC, RCT
 	
24 weeks
 	
Primary: N=500
Ex-primary: N=105
	1. Combination tadalafil and ambrisentan
	2. Monotherapy (either tadalafil or ambrisentan)
	3. All patients on treatment
		Treatment-naïve PAH with WHO functional class II or III	Patients with a first adjudicated clinical failure event* over 24 weeks in patients enrolled before and after protocol amendment (ex-primary vs. primary analysis).
			
			Protocol amendment required higher pulmonary vascular resistance and excluded patients with ≥3 risk factors for HFpEF including DM, HTN, obesity, or history of any CAD.
				Primary analysis (without risk factors for HFpEF) vs. ex-primary analysis (with risk factors):
				Clinical failure event:
				  1. 46 (18%) vs. 14 (29%) (combination)
				  2. 77 (31%) vs. 21 (38%) (monotherapy)
				  3. 123 (25%) vs. 35 (33%) (all)
				Discontinuation due to adverse events:
				  1. 14% vs. 33% (combination)
				  2. 15% vs. 23% (tadalafil)
				  2. 19% vs. 38% (ambrisentan)
				  3. 16% vs. 31% (all)
				Serious adverse events:
				  1. 36% vs. 57% (combination)
				  2. 36% vs. 58% (ambrisentan)
				  2. 41% vs. 43% (tadalafil)
				  3. 37% vs. 53% (all)
				For both combination and monotherapy, clinical failure events were more common in patients with cardiovascular risk factors and associated with increased adverse events. Clinical failure was driven primarily by hospitalization due to PAH.

White, et al. AMBITION[36]
 	
Prespecified subgroup analysis of a DB, MC, RCT
 	
24 weeks
 	
N=500
	1. Combination tadalafil and ambrisentan
	2. Monotherapy (either tadalafil or ambrisentan)
	
	Functional class II N= 155
	Functional class III N=345
		Treatment-naïve PAH with WHO functional class II or III
		
		Patients with ≥ 3 cardiovascular risk factors for HFpEF were excluded
			Patients with an adjudicated clinical failure event* over 24 weeks in patients with functional class II or III symptoms	Functional class II:
				  1. 4 (5%)
				  2. 17 (22%)
				1 vs. 2: HR 0.21; 95% CI 0.071 to 0.63
				
				Functional class III:
				  1. 42 (24%)
				  2. 60 (36%)
				1 vs. 2: HR 0.58; 95% CI 0.39 to 0.86
				
				In patients without risk factors for HFpEF, clinical failure events were less common in patients treated with combination therapy compared to monotherapy for patients with either functional class II or III symptoms.

*Clinical failure included death, hospitalization for PAH, ≥15% decline in 6MWD and change in WHO functional status over 14 days, or any decline in 6MWD and WHO functional status over 6 months.

Abbreviations: 6MWD = 6 minute walk distance; CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension; MC = multicenter; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; OL = open-label; OR = odds ratio; PAH = pulmonary arterial hypertension; PDE-5 inhibitor = phosphodiesterase-5 inhibitor; RCT = randomized clinical trial; TID = three times daily; WHO = world health organization

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Appendix 1: Current Preferred Drug List

Pulmonary Arterial Hypertension Oral and Inhaled Drugs

Generic	Brand	Form	PDL
bosentan	BOSENTAN	TABLET	Y
bosentan	TRACLEER	TABLET	Y
sildenafil citrate	REVATIO	TABLET	Y
sildenafil citrate	SILDENAFIL CITRATE	TABLET	Y
ambrisentan	AMBRISENTAN	TABLET	N
ambrisentan	LETAIRIS	TABLET	N
bosentan	TRACLEER	TAB SUSP	N
iloprost tromethamine	VENTAVIS	AMPUL-NEB	N
macitentan	OPSUMIT	TABLET	N
riociguat	ADEMPAS	TABLET	N
selexipag	UPTRAVI	TAB DS PK	N
selexipag	UPTRAVI	TABLET	N
sildenafil citrate	REVATIO	SUSP RECON	N
sildenafil citrate	SILDENAFIL CITRATE	SUSP RECON	N
sildenafil citrate	SILDENAFIL CITRATE	TABLET	N
sildenafil citrate	VIAGRA	TABLET	N
tadalafil	ADCIRCA	TABLET	N
tadalafil	ALYQ	TABLET	N
tadalafil	TADALAFIL	TABLET	N
treprostinil	TYVASO	AMPUL-NEB	N
treprostinil diolamine	ORENITRAM ER	TABLET ER	N
treprostinil/neb accessories	TYVASO REFILL KIT	AMPUL-NEB	N
treprostinil/nebulizer/accesor	TYVASO INSTITUTIONAL START KIT	AMPUL-NEB	N
treprostinil/nebulizer/accesor	TYVASO STARTER KIT	AMPUL-NEB	N

Pulmonary Arterial Hypertension Parenteral Drugs

Generic	Brand	Form	PDL
epoprostenol sodium (glycine)	EPOPROSTENOL SODIUM	VIAL	Y
epoprostenol sodium (glycine)	FLOLAN	VIAL	Y
epoprostenol sodium	EPOPROSTENOL SODIUM	VIAL	N
epoprostenol sodium	VELETRI	VIAL	N
sildenafil citrate	REVATIO	VIAL	N
sildenafil citrate	SILDENAFIL CITRATE	VIAL	N
treprostinil sodium	REMODULIN	VIAL	N
treprostinil sodium	TREPROSTINIL	VIAL	N

Appendix 2: Abstracts of Comparative Clinical Trials

BACKGROUND: Riociguat and phosphodiesterase-5 inhibitors (PDE5i), approved for the treatment of pulmonary arterial hypertension (PAH), act on the same pathway via different mechanisms. Riociguat might be an alternative option for patients with PAH who do not respond sufficiently to treatment with PDE5i, but comparisons of the potential benefits of riociguat and PDE5i in these patients are needed. The aim of this trial was to assess the effects of switching to riociguat from PDE5i therapy versus continued PDE5i therapy in patients with PAH at intermediate risk of 1-year mortality.
METHODS: Riociguat rEplacing PDE5i therapy evaLuated Against Continued PDE5i thErapy (REPLACE) was an open-label, randomised controlled trial in 81 hospital-based pulmonary hypertension centres in 22 countries. The study enrolled patients aged 18-75 years with symptomatic PAH at intermediate risk of 1-year mortality (based on the European Society for Cardiology-European Respiratory Society guideline thresholds for WHO functional class and 6-min walk distance [6MWD]) who were receiving treatment with a PDE5i with or without an endothelin receptor antagonist for at least 6 weeks before randomisation. Patients were excluded if they had been previously treated with riociguat, had used prostacyclin analogues or prostacyclin receptor agonists within 30 days before randomisation, had clinically significant restrictive or obstructive parenchymal lung disease, or had left heart disease. Patients were randomly assigned (1:1) to remain on PDE5i treatment (oral sildenafil [>=60 mg per day] or oral tadalafil [20-40 mg per day]; the PDE5i group) or to switch to oral riociguat (up to 2.5 mg three times per day; the riociguat group), using an interactive voice and web response system, stratified by cause of PAH. The primary endpoint was clinical improvement by week 24, defined as an absence of clinical worsening and prespecified improvements in at least two of three variables (6MWD, WHO functional class, and N-terminal prohormone of brain natriuretic peptide), analysed using last observation carried forward in all randomly assigned patients with observed values at baseline and week 24 who received at least one dose of study medication (the full analysis set). Secondary endpoints included clinical worsening events. The trial has been completed and is registered with ClinicalTrials.gov, NCT02891850.
FINDINGS: Between Jan 11, 2017, and July 31, 2019, 293 patients were screened, of which 226 patients were randomly assigned to the riociguat group (n=111) or to the PDE5i group (n=115). 211 patients completed the study and 14 patients discontinued (seven in each group). One patient assigned to the PDE5i group did not receive treatment, so 225 patients were included in the safety analysis, and one further patient in the PDE5i group had missing components of the composite primary endpoint at baseline, so 224 patients were included in the full analysis set. The primary endpoint was met by 45 (41%) of 111 patients in the riociguat group and 23 (20%) of 113 patients in the PDE5i group; odds ratio [OR] 2.78 (95% CI 1.53-5.06; p=0.0007). Clinical worsening events occurred in one (1%) of 111 patients in the riociguat group (hospitalisation due to worsening PAH) and 10 (9%) of 114 patients in the PDE5i group (hospitalisation due to worsening PAH [n=9]; disease progression [n=1]; OR 0.10 [0.01-0.73]; p=0.0047). The most frequently occurring adverse events were hypotension (15 [14%]), headache (14 [13%]), and dyspepsia (10 [9%]) in the riociguat group, and headache (eight [7%]), cough (seven [6%]), and upper respiratory tract infection (seven [6%]) in the PDE5i group. Serious adverse events were reported in eight (7%) of 111 patients in the riociguat group and 19 (17%) of 114 patients in the PDE5i group. During the study, four patients died in the PDE5i group, one of them during the safety follow-up period.
INTERPRETATION: Switching to riociguat from PDE5i treatment, both of which act via the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate pathway, could be a strategic option for treatment escalation in patients with PAH at intermediate risk of 1-year mortality.,
FUNDING: Bayer AG, Merck Sharp & Dohme. Copyright © 2021 Elsevier Ltd. All rights reserved.

McLaughlin VV, Vachiery J-L, Oudiz RJ, et al. Patients with pulmonary arterial hypertension with and without cardiovascular risk factors: Results from the AMBITION trial. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation.* 2019;38(12):1286-1295.

BACKGROUND: The purpose of this study was to compare patients with pulmonary arterial hypertension enrolled in the AMBITION trial with (excluded from the primary analysis set [ex-primary analysis set]) and without (primary analysis set) multiple risk factors for left ventricular diastolic dysfunction.
METHODS: Treatment-naive patients with pulmonary arterial hypertension were randomized to once-daily ambrisentan and tadalafil combination therapy, ambrisentan monotherapy, or tadalafil monotherapy. The primary end point was time from randomization to first adjudicated clinical failure event.
RESULTS: Primary analysis set patients (n=500), compared with ex-primary analysis set patients (n=105), were younger (mean, 54.4 vs 62.1 years) with greater baseline 6-minute walk distance (median, 363.7 vs 330.5 meters) and fewer comorbidities (e.g., hypertension and diabetes). Treatment effects of initial combination therapy vs pooled monotherapy were directionally the same for both populations, albeit of a lower magnitude for ex-primary analysis set patients. Initial combination therapy reduced the risk of clinical failure compared with pooled monotherapy in primary analysis set patients (hazard ratio, 0.50; 95% confidence interval, 0.35-0.72), whereas the effect was less clear in ex-primary analysis set patients (hazard ratio, 0.70; 95% confidence interval, 0.35-1.37). Overall, primary analysis set patients had fewer clinical failure events (25% vs 33%), higher rates of satisfactory clinical response (34% vs 24%), and lower rates of permanent study drug withdrawal due to adverse events (16% vs 31%) than ex-primary analysis set patients.
CONCLUSIONS: Efficacy of initial combination therapy vs pooled monotherapy was directionally similar for primary analysis set and ex-primary analysis set patients. However, ex-primary analysis set patients (with multiple risk factors for left ventricular diastolic dysfunction) experienced higher rates of clinical failure events and the response to combination therapy vs monotherapy was attenuated. Tolerability was better in primary analysis set than ex-primary analysis set patients. Copyright © 2019 International Society for Heart and Lung Transplantation. Published by Elsevier Inc. All rights reserved.

White RJ, Vonk-Noordegraaf A, Rosenkranz S, et al. Clinical outcomes stratified by baseline functional class after initial combination therapy for pulmonary arterial hypertension. *Respiratory research.* 2019;20(1):208.

BACKGROUND: Initial combination therapy with ambrisentan and tadalafil reduced the risk of clinical failure events for treatment-naive participants with pulmonary arterial hypertension (PAH) as compared to monotherapy. Previous studies in PAH have demonstrated greater treatment benefits in more symptomatic participants.
METHODS: AMBITION was an event-driven, double-blind study in which participants were randomized 2:1:1 to once-daily initial combination therapy with ambrisentan 10 mg plus tadalafil 40 mg, ambrisentan 10 mg plus placebo, or tadalafil 40 mg plus placebo. In this pre-specified subgroup analysis, we compared the efficacy data between those with functional class (FC) II vs. FC III symptoms at baseline.
RESULTS: This analysis included 500 participants in the previously defined primary analysis set (n = 155 FC II, n = 345 FC III). Comparing combination therapy to pooled monotherapy, the risk of clinical failure events was reduced by 79% (hazard ratio, 0.21 [95% confidence interval: 0.071, 0.63]) for FC II patients and 42% (hazard ratio, 0.58 [95% confidence interval: 0.39, 0.86]) for FC III patients. In a post-hoc analysis, the risk of first hospitalization for worsening PAH was also reduced by combination therapy, particularly for FC II patients (0 combination vs. 11 [14%] pooled monotherapy). Adverse events were frequent but comparable between the subgroups.

CONCLUSIONS: Treatment benefit from initial combination therapy appeared at least as great for FC II as for FC III participants. Hospitalizations for worsening PAH were not observed in FC II participants assigned to combination. The present data support an initial combination strategy for newly diagnosed patients even when symptoms are less severe. Funded by Gilead Sciences, Inc. and GlaxoSmithKline; AMBITION ClinicalTrials.gov number, NCT01178073.

Appendix 3: Medline Search Strategy
Ovid MEDLINE(R) ALL 1946 to July 30, 2021

1	Bosentan/	1749
2	Sildenafil Citrate/	5568
3	ambrisentan.mp.	453
4	exp Endothelin Receptor Antagonists/	5925
5	Iloprost/	2063
6	macitentan.mp.	338
7	riociguat.mp.	414
8	selexipag.mp.	178
9	Tadalafil/	1511
10	exp Phosphodiesterase 5 Inhibitors/	8568
11	treprostinil.mp.	648
12	Epoprostenol/	12735
13	exp Prostaglandins/	101597
14	exp Hypertension, Pulmonary/	38215
15	exp Lung Diseases, Interstitial/	57966
16	14 or 15	95464
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	115628
18	16 and 17	4566

19	limit 18 to (english language and humans)	3444
20	limit 19 to yr="2018 -Current"	457
21	limit 20 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	107

Appendix 4: Key Inclusion Criteria

Population	Patients with pulmonary hypertension
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1
Outcomes	Symptom improvement, exercise capacity, lung function, hospitalizations, mortality
Setting	Outpatient

Injectable Pulmonary Arterial Hypertension Agents (IV/SC)

Goals:

- Restrict use to patients with pulmonary arterial hypertension (PAH) and World Health Organization (WHO) Functional Class III-IV symptoms.

Length of Authorization:

- Up to 12 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber consider a change to a preferred product? Note: preferred products do not require PA.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #4
4. Is there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1; ICD 10 I27.0)? Note: injectable PAH medications are not FDA-approved for other forms of pulmonary hypertension.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria

5. Is the patient classified as having World Health Organization (WHO) Functional Class III-IV symptoms?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Oral/Inhaled Pulmonary Hypertension Agents

Goals:
- Restrict use to appropriate patients with World Health Organization (WHO) Functional Class II-IV symptoms and WHO pulmonary classifications with demonstrated clinical benefit in clinical trials (e.g., pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension, or interstitial lung disease),.
- Restrict use to conditions funded by the Oregon Health Plan (OHP). Note: erectile dysfunction is not funded by the OHP.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred drugs

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the drug being prescribed by a pulmonologist or cardiologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for riociguat (Adempas®) or ambrisentan (Letairis®)?	**Yes:** Go to #5	**No:** Go to #6
5. Is there documentation that the patient has a medical history of PAH associated with idiopathic interstitial pneumonias or idiopathic pulmonary fibrosis?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1; ICD10 I27.0)?	**Yes:** Go to #8	**No:** Go to #9
8. Will the prescriber consider a change to a preferred product? Note: preferred products do not require PA.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Approve for 12 months
9. Is the request for riociguat in a patient with a diagnosis of chronic thromboembolic pulmonary hypertension (WHO Group 4; ICD10 I27.24)?	**Yes:** Approve for 12 months	**No:** Go to #10
10. Is the request for nebulized treprostinil (Tyvaso®) in a patient with a diagnosis of interstitial lung disease (WHO Group 3; ICD10 I27.23)? Note: treprostinil has not been studied and is not recommended in patients with pulmonary hypertension due to chronic obstructive pulmonary disease.	**Yes:** Approve for 12 months	**No:** Go to #11

Approval Criteria		
11. RPh Only: Prescriber must provide supporting literature for use.	**Yes:** Approve for length of treatment.	**No:** Deny; not funded by the OHP