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Drug Class Update: Pulmonary Hypertension

Date of Review: September 2018

Date of Last Review: March 2016
Dates of Literature Search: 11/01/2015-06/26/2018

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

Purpose for Class Update: To evaluate new comparative evidence of drug therapy for pulmonary hypertension (PH). PH is classified into 5 specific types. Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are the only types of PH with targeted drug therapies and will be the focus of this report.

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?
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 (World Health Organization [WHO] functional class) or other disease characteristics that may benefit more from a specific drug or combination of drugs?

Conclusions:
- There is no new direct comparative evidence for drug treatment of PAH or CTEPH.
- The American Heart Association and American Thoracic Society guidelines for pediatric pulmonary hypertension were updated in November 2015. Due to limited data available in pediatric patients, primary recommendations were made based on limited populations from single randomized controlled trials (RCTs) or non-randomized studies (level of evidence B). Intravenous or subcutaneous prostanoids or its analogs are recommended for high-risk patients with PAH (Class I, level of evidence B).[1] In low-risk patients, oral PAH-targeted therapy is recommended and should include a phosphodiesterase (PDE)-5 inhibitor or an endothelin receptor antagonists (ERA; Class I, level of evidence B).[1]
- A new formulation of bosentan (Tracleer®), an oral dispersible tablet, was approved by the United States Food and Drug Administration (FDA) in September 2017. Bosentan also received an expanded indication for PAH in pediatric patients at least 3 years of age.
- There have been new safety labeling updates for 8 products since the previous review. Contraindications for riociguat were updated to include idiopathic interstitial pneumonias and more specific language was added surrounding drug interactions with PDE-5 inhibitors. Selexipag labeling was updated to include contraindications with concomitant CYP2C8 inhibitors. Labeling of other products was updated to include more information about adverse effects

for the following: elevated liver enzymes with bosentan, peripheral edema with macitentan, visual loss with PDE-5 inhibitors, and symptomatic hypotension and bleeding risk with injectable and inhaled treprostinil.[2] Monitoring for these adverse effects is recommended.

Recommendations:

- Update prior authorization (PA) criteria to include contraindications for riociguat in patients with idiopathic interstitial pneumonias.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

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 6 minute walking distance (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 [IV] or subcutaneous [SC] 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.[3] Pooled data based on drug class has suggested that oral phosphodiesterase inhibitors and IV epoprostanil 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.[3] Oral and inhalation therapies have been considered an appropriate option for class II-IV patients but do not necessarily negate the need for IV or SC prostycyclins. Preferred oral formulations include bosentan and sildenafil. Historically, IV 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 IV formulation.[3,4]

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. IV 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 25 mmHg at rest.[5,6] PH is classified into 5 groups: pulmonary arterial hypertension (PAH; World Health Organization [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).[5,6] Each type of PH has a unique etiology, pathology and management strategy. PAH and CTEPH are the only types of PH with specific targeted drug therapies and will be the focus of this report. 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.[6] The exact incidence of CTEPH in the US is unclear.[7] In the Oregon Health Plan (OHP) fee-for-service (FFS) population, approximately 700 patient had a diagnosis of primary pulmonary hypertension from 2016-2017. Over the last quarter in 2017, there were approximately 50 OHP FFS patients with claims for PAH-specific medications with the majority of use for preferred drugs.

PAH can also be classified based on the WHO functional status which divides PAH 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).[5,6] Symptoms primarily include respiratory dyspnea, syncope, chest pain, exercise intolerance, and peripheral edema. The estimated 3 year survival is 58-73% with worsening prognosis for patients with higher New York Heart Association (NYHA) functional class, rapidly progressive disease, need for prostanoid therapy, or recurrent hospitalizations.[5] 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.[1,6]

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.[6] Other supportive care includes oxygen, supervised physical activity, and rehabilitation.[6] 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
- ERAs: bosentan, macitentan, and ambrisentan
- prostacyclin receptor agonists: selexipag
- soluble guanylate cyclase stimulators: riociguat
- prostanoids: epoprostenol, treprostinil, and iloprost

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 75-92% at 6 years after surgery.[6,7] However, not all patients are eligible for surgery, and the disease either recurs or is refractory to surgery in 5-35% of cases.[5] 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.[7] However, recommendations are supported by limited evidence such as small RCTs, non-randomized studies, indirect evidence, or lack of clinical outcome data.[7]

Goals of therapy 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 in 6MWD have not demonstrated any correlation with mortality reduction or disease progression for patients with PAH.[8] Patients with 6MWD greater than 440 to 500 meters are generally considered to be at low risk for clinical events.[1,6] A minimum clinically important change in 6MWD has not been established and improvements of up to 15% change in 6MWD over 1 year have not been correlated with increased survival compared to patients with no change in 6MWD.[8] Clinical worsening is a composite endpoint often defined as time to change in WHO functional class, initiation of treatment with IV or SC prostanoids, all-cause mortality, heart or lung transplant, or atrial septostomy.[9]

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), the Cochrane Collaboration, National Institute for

Health and Clinical Excellence (NICE), Department of Veterans Affairs, Institute for Clinical and Economic Review (ICER), 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 Cochrane review examining the efficacy of riociguat for PH was published in 2016.[5] Five RCTs (n=966) were included in the review and only 3 had data suitable for a pooled analysis.[5] Included studies had low risk of selection bias and unclear performance and detection bias. Attrition bias was low for 3 included studies and all trials were sponsored by the drug manufacturer.[5] Exercise capacity as evaluated by mean change in the 6MWD for patients with PH was 30.13 meters (95% CI 5.29 to 54.96) compared to placebo with significant heterogeneity (I^2=64%).[5] There was no statistical difference between riociguat and placebo for outcomes of mortality (OR 0.57, 95% CI 0.18 to 1.80), change in WHO functional class (OR 1.53, 95% CI 0.87 to 2.72), time to clinical worsening (OR 0.45, 95% CI 0.17 to 1.14), or serious adverse events (OR 1.12, 95% CI 00.66 to 1.90).[5] Subgroup analyses were evaluated based on type of PH. Two studies evaluated outcomes for PAH and a single study evaluated patients with CTEPH. In patients with CTEPH, compared to placebo riociguat had a statistical significant difference for improvement in WHO functional class (33% vs. 15%; OR 2.80, 95% CI 1.43 to 5.46) and exercise capacity (45 m, 95% CI 23.87 to 66.12) but not mortality, clinical worsening, or serious adverse events.[5] In patients with PAH, clinical worsening was statistically better than placebo (1.2% vs. 6.4%, OR 0.18, 95% CI 0.05 to 0.68), but outcomes of mortality, exercise capacity, change in WHO functional status, and serious adverse events were not statistically different.[5]

After review, 9 systematic reviews were excluded due to poor methodological quality, wrong study design of included trials (e.g., observational), analytical methods (e.g., network meta-analyses), comparator (e.g., no control), population (non-United States), setting (inpatient), or outcome studied (e.g., non-clinical).

New Guidelines:

Guidelines Which Met Quality Standards:

American Heart Association and American Thoracic Society

The American Heart Association and American Thoracic Society guidelines for pediatric pulmonary hypertension were updated in November 2015.[1] The guideline committee acknowledged that data in children was lacking or was often based on observational studies or extrapolated from experience in adults.[1] The majority of pharmacologic recommendations were either made based on limited populations from single RCTs or non-randomized studies (level of evidence B) or consensus opinion, case studies, or standard of care (level of evidence C).[1] Of the guideline and writing committee, 11 of the 27 members disclosed funding from pharmaceutical manufacturers for research grants, speaking honoraria, or consulting.[1] Four members had funding which was considered "significant" defined as greater than $10,000 or more than 5% of the individual's gross income.[1]

Recommendations were made for patients considered low-risk and high-risk based on disease severity. Patients were considered high-risk if they had clinical evidence of right ventricular failure, pericardial effusion, WHO Class III-IV, recurrent syncope, significantly elevated BNP, 6MWD less than 300 meters, peak volume of oxygen during cardiopulmonary testing less than 15 mL/kg/min, or hemodynamics indicating severe disease.[1] Intravenous or subcutaneous prostacyclin or its analogs are recommended for high-risk patients (Class I, level of evidence B).[1] In low-risk patients, oral PAH-targeted therapy is recommended and should include a phosphodiesterase inhibitor or an ERA (Class I, level of evidence B).[1] Oral phosphodiesterase inhibitors may also be considered during

inhaled nitric oxide withdrawal.[1] Switching from parenteral to oral/inhaled therapy may be considered for patients with sustained and near-normal pulmonary hemodynamics (Class IIB, level of evidence C).[1] Close monitoring by an experienced pediatric pulmonary hypertension center is recommended upon switching to oral or inhaled therapy. Combination therapy may be considered to achieve therapeutic targets (Class IIa, level of evidence C).[1]

After review, 3 guidelines were excluded due to poor quality.[6,10]

New Formulations or Indications:

A new formulation of bosentan (Tracleer®), an oral dispersible tablet, was approved by the FDA in September 2017. The new formulation is FDA-approved for treatment of PAH in adults and pediatric patients at least 3 years of age.[11] Bosentan oral tablets had previously only been approved for adults with PAH. The expanded indication to pediatric patients was based on efficacy data from an open-label, uncontrolled trial of 19 pediatric patients with WHO functional class II or III.[11] Safety data included 100 pediatric patients treated for a median of 17 months.[11] Hemodynamic improvements including peripheral vascular resistance were similar to parameters observed in adults.[11]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts[2]

Generic Name	Brand Name	Month/Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
Bosentan	Tracleer®	09/2017	Warnings/Precautions	In a pooled analysis of pediatric studies, 2% of patients have elevations in liver aminotransferases >3 times the upper limit of normal (ULN). Avoid initiation of treatment with elevated liver enzymes (>3x ULN). In patients with WHO functional class II, consider whether benefits of treatment outweigh risks of hepatotoxicity. Information regarding embryo-fetal toxicity based on data from animal reproduction studies was added to the labeling. Bosentan is contraindicated in pregnancy and is only available through a REMS program.
Macitentan	Opsumit®	03/2017	Warnings/Precautions	Warnings including peripheral edema and fluid retention were added to product labeling. Patients with concomitant left ventricular dysfunction may be at increased risk for fluid retention and heart failure exacerbations. Monitoring is recommended with treatment discontinuation if clinically appropriate.
Riociguat	Adempas®	01/2017	Contraindications	Riociguat is contraindicated in patients with PAH associated with idiopathic interstitial pneumonias. Labeling also updated to include the following information on drug interactions: avoid riociguat administration within 24 hours of sildenafil use or within 24 hours before or 48 hours after tadalafil use.

Selexipag	Uptravi®	07/2017	Contraindications	Labeling was updated to include contraindications with concomitant use of strong CYP2C8 inhibitors (eg, gemfibrozil).
Sildenafil Tadalafil	Revatio® Adcirca®	07/2017 05/2017	Warnings/Precautions	Labeling was updated to include information concerning visual loss and non-arteritic anterior ischemic optic neuropathy based on information from 2 observational studies. Results indicate a 2-fold increase of optic events upon initiation of a phosphodiesterase inhibitor compared to estimated risk prior to treatment. Estimated annual incidence of non-arteritic anterior ischemic optic neuropathy is 2-12 cases per 100,000 in males greater than 50 years of age.
Treprostinil	Remodulin® Tyvaso®	06/2018 06/2016	Warnings/Precautions	Labeling for Remodulin® was updated to include warnings for symptomatic hypotension and risk of bleeding due to platelet aggregation. Labeling for Tyvaso® was also updated to include risk for bleeding.

Randomized Controlled Trials:

A total of 146 citations were manually reviewed from the initial literature search. After further review, 145 citations were excluded because of wrong study design (eg, observational or post-hoc analyses), setting (inpatient), comparator (eg, no control), or outcome studied (eg, non-clinical). The remaining 1 trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Vizza, et al. 2017.[12] MC, DB, PC RCT N=103	1. Sildenafil 20 mg three times daily 2. Placebo Patients were on stable bosentan therapy for at least 3 months (62.5 or 125 mg BID)	Idiopathic PAH with connective tissue disease	Change in 6-minute walk distance at 12 weeks	Mean change from baseline 1. 13.6 m 2. 14.1 m LSMD -2.4 m (90% CI -21.8 to 17.1 m); p=0.6

Abbreviations: BID = twice daily; DB = double blind; LSMD = least squares mean difference; MC = multicenter; PAH = pulmonary arterial hypertension; PC = placebo controlled; RCT = randomized clinical trial; SD = standard deviation, etc.

References:

1. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. *Circulation.* 2015;132(21):2037-2099.
2. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed June 26, 2018.
3. Drug Use Research & Management Program. Class Update with New Drug Evaluation: Drugs for Pulmonary Arterial Hypertension. March 2016; http://www.orpdl.org/durm/meetings/meetingdocs/2016_03_31/archives/2016_03_31_PAHClassUpdate_ARCHIVE.pdf.
4. Drug Use Research & Management Program. Abbreviated Class Review: Intravenous/subcutaneous pulmnary arterial hypertension agents. September 2012; http://www.orpdl.org/durm/meetings/meetingdocs/2012_09_27/archives/2012_09_27_IV_PAH_CR.pdf.
5. Wardle AJ, Seager MJ, Wardle R, et al. Guanylate cyclase stimulators for pulmonary hypertension. *The Cochrane database of systematic reviews.* 2016(8):CD011205.
6. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016;37(1):67-119.
7. Chronic thromboembolic pulmonary hypertension (CTEPH). DynaMed [internet database]. Ipswich, MA: EBSCO Publishing. Updated May 2, 2016. Accessed July 6, 2018.
8. Farber HW, Miller DP, McGoon MD, et al. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *J Heart Lung Transplant.* 2015;34(3):362-368.
9. Tran K CK, Jabr M, Coyle D, Boucher M, Mielniczuk L. Drugs for pulmonary arterial hypertension: comparative efficacy, safety, and cost-effectiveness. *Canadian Agency for Drugs and Technologies in Health.* March 2015.
10. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis.* 2017;76(8):1327-1339.
11. Tracleer (bosentan) tablets [package labeling]. San Francisco, CA: Actelion Pharmaceuticals; September 2017.
12. Vizza CD, Jansa P, Teal S, et al. Sildenafil dosed concomitantly with bosentan for adult pulmonary arterial hypertension in a randomized controlled trial. *BMC cardiovascular disorders.* 2017;17(1):239.

Appendix 1: Current Preferred Drug List

PAH Oral and Inhaled Drugs

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

PAH Parenteral Drugs

Generic	Brand	FormDesc	Route	PDL
epoprostenol sodium (glycine)	EPOPROSTENOL SODIUM	VIAL	INTRAVEN	Y
epoprostenol sodium (glycine)	FLOLAN	VIAL	INTRAVEN	Y
epoprostenol sodium (arginine)	VELETRI	VIAL	INTRAVEN	N
sildenafil citrate	REVATIO	VIAL	INTRAVEN	N
sildenafil citrate	SILDENAFIL CITRATE	VIAL	INTRAVEN	N
treprostinil sodium	REMODULIN	VIAL	INJECTION	N

Appendix 2: Abstracts of Comparative Clinical Trials

Vizza CD, Jansa P, Teal S, Dombi T, Zhou D. Sildenafil dosed concomitantly with bosentan for adult pulmonary arterial hypertension in a randomized controlled trial. BMC cardiovascular disorders. 2017;17(1):239.

BACKGROUND: Few controlled clinical trials exist to support oral combination therapy in pulmonary arterial hypertension (PAH). METHODS: Patients with PAH (idiopathic [IPAH] or associated with connective tissue disease [APAH-CTD]) taking bosentan (62.5 or 125 mg twice daily at a stable dose for >=3 months) were randomized (1:1) to sildenafil (20 mg, 3 times daily; n = 50) or placebo (n = 53). The primary endpoint was change from baseline in 6-min walk distance (6MWD) at week 12, assessed using analysis of covariance. Patients could continue in a 52-week extension study. An analysis of covariance main-effects model was used, which included categorical terms for treatment, baseline 6MWD (<325 m; >=325 m), and baseline aetiology; sensitivity analyses were subsequently performed. RESULTS: In sildenafil versus placebo arms, week-12 6MWD increases were similar (least squares mean difference [sildenafil-placebo], -2.4 m [90% CI: -21.8 to 17.1 m]; P = 0.6); mean +/- SD changes from baseline were 26.4 +/- 45.7 versus 11.8 +/- 57.4 m, respectively, in IPAH (65% of population) and -18.3 +/- 82.0 versus 17.5 +/- 59.1 m in APAH-CTD (35% of population). One-year survival was 96%; patients maintained modest 6MWD improvements. Changes in WHO functional class and Borg dyspnoea score and incidence of clinical worsening did not differ. Headache, diarrhoea, and flushing were more common with sildenafil. CONCLUSIONS: Sildenafil, in addition to stable (>=3 months) bosentan therapy, had no benefit over placebo for 12-week change from baseline in 6MWD. The influence of PAH aetiology warrants future study. TRIAL REGISTRATION: ClinicalTrials.gov NCT00323297 (registration date: May 5, 2006).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to June 20, 2018

1	exp Hypertension, Pulmonary/	32511
2	exp Endothelin Receptor Antagonists/	4694
3	bosentan.mp.	2459
4	exp Sildenafil Citrate/	4975
5	ambrisentan.mp.	345
6	exp Tadalafil/	1206
7	exp Phosphodiesterase 5 Inhibitors/	7335
8	exp prostaglandins/ or exp prostaglandins i/ or exp epoprostenol/ or exp prostaglandins, synthetic/ or exp iloprost/	97655
9	macitentan.mp.	211
10	treprostinil.mp.	485
11	selexipag.mp.	91
12	riociguat.mp.	248
13	exp Guanylate Cyclase-Activating Proteins/	223
14	guanylate cyclase/ or exp soluble guanylyl cyclase/	7123
15	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	117224
16	1 and 15	4091
17	limit 16 to (english language and humans)	3019
18	limit 17 to yr="2015 -Current"	476
19	limit 18 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 multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	146

Appendix 4: Key Inclusion Criteria

Population	Patients with pulmonary artery hypertension (United States population)
Intervention	Drugs listed in **Appendix 1**
Comparator	Active or placebo comparisons of drugs listed in **Appendix 1**.
Outcomes	1) Mortality 2) Hospitalizations 3) Heart or lung transplant 4) Atrial septostomy 5) Change in WHO functional class or functional status 6) Exercise capacity
Timing	Any study duration; literature search from 11/01/2015 to 06/26/2018
Setting	Outpatient

Oral/Inhaled Pulmonary Arterial Hypertension Agents

Goals:

- Restrict use to appropriate patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension and World Health Organization (WHO) Functional Class II-IV symptoms.
- 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.	
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 there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1; ICD10 I27.0)?	**Yes:** Go to #9	**No:** Go to #5
5. Is there a diagnosis of chronic thromboembolic pulmonary hypertension (WHO Group 4; ICD10 I27.24)?	**Yes:** Go to #6	**No:** Go to #11
6. Is the request for riociguat (Adempas®)?	**Yes:** Go to #7	**No:** Go to #11
7. Is there documentation that the patient has a medical history of PAH associated with idiopathic interstitial pneumonias?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8

Approval Criteria		
8. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
9. 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 #10
10. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
11. RPh Only: Prescriber must provide supporting literature for use.	**Yes:** Approve for length of treatment.	**No:** Deny; not funded by the OHP

P&T Review: *9/18 (SS); 3/16; 7/14; 3/14; 2/12; 9/10*
Implementation: *TBD; 10/13/16; 5/1/16; 5/14/12; 1/24/12; 1/1/11*

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 (pharmacy and physician administered claims)

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.
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.

Approval Criteria		
6. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *9/18 (SS); 3/16; 9/12*
Implementation: *10/13/16; 1/1/13*