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Abbreviated Class Update: Oral/Inhalation Pulmonary Arterial Hypertension (PAH) Agents

Month/Year of Review: July 2014
Last Review: 2009 PAH Agents
2012 IV PAH Agents

End date of literature search: May 2014
Source Document: Provider Synergies
OSU DURM

New drugs reviewed: macitentan (Opsumit®) and riociguat (Adempas®)
New drug formulation reviewed: oral treprostinil (Orenitram®)

Current PDL Status:

Preferred

Drug Class	Drug
Endothelin Antagonist	**Bosentan**
Phosphodiesterase-5 Inhibitor	**Sildenafil citrate**

Non-preferred

Drug Class	Drug
Prostanoid	**Treprostinil (inhaled)**
Prostanoid	**Iloprost (inhaled)**
Phosphodiesterase-5 Inhibitor	**Tadalafil**
Endothelin Antagonist	**Ambrisentan**

Research Questions:

- Are macitentan, riociguat and/or oral treprostinil more effective than preferred PDL treatments for patients with pulmonary arterial hypertension (PAH)?
- Are macitentan, riociguat and/or oral treprostinil a safer alternative to preferred PDL treatments for patients with PAH?
- Are there indications or subpopulations where macitentan, riociguat and/or oral treprostinil may be more effective or safer than other available agents?
- Are there new guidelines and/or evidence that suggest that changes should be made to the PAH agents on the PDL?

Conclusions:

- There is insufficient evidence to directly compared riociguat to other PAH treatments. There is moderate strength of evidence that riociguat improved the 6 minute walk (6MW) distance in patients with chronic thrombotic/embolic disease (CTEPH) and low to moderate evidence in patients with PAH. Changes in 6MW distance ranged from 33 to 39 m, which is at the lower end of clinically significant improvement and consistent with PDE-5 inhibitors, which work by a similar mechanism of action. Adverse events, such as syncope and hypotension, are similar to other vasodilators.[1,2]
- There is no direct comparative evidence evaluating macitentan to other PAH treatments. There is moderate strength of evidence that macitentan improves the composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with IV or SQ prostanoids or worsening of PAH in patients with PAH based on one small study lasting approximately 2 years. This was primarily driven by worsening of PAH. Modest efficacy was demonstrated in the 6MW distance at 6 months with a treatment effect of 22m for the macitentan 10mg group. Patients on background PAH treatment and those with functional class III/IV symptoms received the most benefit from treatment. Common adverse events are anemia, headache and nasopharyngitis.[3]
- Studies comparing oral treprostinil to other PAH therapies are lacking. There is low strength of evidence that oral treprostinil improves the 6MW distance in patients not on other vasodilatory therapy for PAH compared to placebo, 26 m and 0 m, respectively.[4] Oral treprostinil use in patients taking other PAH therapies demonstrated no significant difference in the 6MW distance when compared to placebo. Oral treprostinil was associated with headache, nausea and diarrhea in clinical trials.[4,5,6]
- There is no new significant comparative evidence on other treatments for PAH. Evaluation of recent literature supports the current PDL placement of agents for PAH.

Recommendations:

- Prior authorize riociguat to ensure appropriate use by qualified providers (Appendix 2).
- Prior authorize macitentan to ensure appropriate use by qualified providers. Limited evidence is insufficient to prefer macitentan over bosentan for placement on PDL.
- Prior authorize oral treprostinil to ensure appropriate use by qualified providers.
- Continue to include an agent from each class on the PDL and evaluate comparative costs in executive session.

Reason for Review:

This review will update the recommendations for oral and inhalation treatments for PAH. Since the last review additional systematic reviews and guidelines have been published. New PAH treatments have also been approved. This review will analyze the comparative effectiveness of the PAH treatments and incorporate important updates and revisions as they are related to this class since the last review.

Previous Conclusions/February 2012:

- Comparative evidence was insufficient to preference one agent over another.
- An agent from each class should be offered for coverage (bosentan and sildenafil are on the PDL).

Background:

PAH is the result of constricted flow through the pulmonary vasculature resulting in increased pulmonary resistance. PAH is defined as a mean pulmonary artery pressure (mPAP) >25 mm Hg with a pulmonary capillary wedge pressure (PCWP), left atrial pressure or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units.[7] The cause of PAH is not fully understood but includes idiopathic, heritable (often from a mutation in

the bone morphogenic protein receptor-2), drug and toxin induced or PAH caused by an underlying medical condition (e.g. connective tissue diseases and HIV infection).[8] Regardless of the etiology, PAH is usually progressive with the most common cause of death being right ventricular failure.[9]

Changes in vascular structure and function within the pulmonary arteries account for the common symptoms of PAH including dyspnea, syncope, fatigue, edema and others. Exercise tolerance, as measured by the 6 minute walk (6MW) distance, and hemodynamic improvements are indicators of survival.[7] The 6MW is the most common outcome measured, which reflects the distance walked in meters. The 6MW distance is a measure of functional status and has been shown to correlate with morbidity and mortality in some studies but recent data suggests a lack of correlation between the 6MW distance and clinical outcomes.[10,11] The inability to detect treatment changes in patients with less severe PAH and to identify treatment differences when trials are short and have small sample sizes are some of the limitations of the 6MW distance as a surrogate endpoint. In PAH trials the minimum meaningful clinical improvement has been shown with a 6MW distance of 33 m.[12,13] Studies of PAH agents have demonstrated 6MW distance improvements of 33-50 m.[7] Other outcomes measured in clinical trials are: mortality, World Health Organization (WHO) functional class changes, hospitalizations, changes in pulmonary vascular resistance, dyspnea (assessed by Borg dyspnea score), and quality of life. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels have been shown to correlate with the presence of PAH but it is unknown if these levels can be used to help manage PAH treatment.[7] Baseline functional class and combined clinical events (i.e. hospitalizations, mortality and rescue treatments) are recommended, in addition to the 6MW distance, to determine effectiveness of PAH therapies.[14]

The World Health Organization classifies pulmonary hypertension (PH) into five groups based on etiology. WHO Group 1 includes PAH caused by idiopathic PAH (IPAH), heritable PAH, and PAH as a result of connective tissue diseases, HIV and portal hypertension. These same groups of PAH were formerly referred to as primary pulmonary hypertension (Table 1).[9] Group 4 PAH caused by CTEPH will also be covered in this review. PH caused by other secondary sources are included in Groups 2, 3 and 5 and won't be the focus of this review. The WHO functional assessment classification system for PH has been adapted from the New York Heart Association (NYHA) functional classification. Both systems are utilized in guidelines and studies to classify patients based on symptoms as well as for treatment guidance (Table 2).[15]

Table 1. Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)[9]

WHO Group 1: Pulmonary Arterial Hypertension	
1. Pulmonary arterial Hypertension	1.4 Associated with
1.1 Idiopathic PAH (IPAH)	1.4.1 Connective tissue diseases
1.2 Heritable	1.4.2 HIV infection
1.2.1 Bone morphogenetic protein receptor (BMPR) type 2	1.4.3 Portal hypertension
1.2.2 Activin receptor-like kinase 1 (ALK1) endoglin (with or without hereditary hemorrhagic telangiectasia)	1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
1.2.3 Unknown	1.4.6 Chronic hemolytic anemia
1.3 Drug induced	1.5 Persistent pulmonary hypertension of the newborn 1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
WHO Group 4: Pulmonary Arterial Hypertension	
4. Chronic thromboembolic pulmonary hypertension (CTEPH)	

Table 2. WHO Functional Assessment Classification[15]

Class	**Description**

Author: Kathy Sentena, Pharm.D.

I	Patients with PH with no limitation in physical ability
II	Patients with PH with slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
III	Patients with PH with marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain or near-syncope
IV	Patients with PH unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest

Significant advances in therapeutic options to treat WHO Group 1 PAH have evolved over the last 15 years including the use of combination therapy. Patients with symptomatic PAH are provided treatment based on functional class. Standard treatment options include: anticoagulants, diuretics, digoxin, and oxygen.[16] PAH-specific therapies are: prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (ERAs) (bosentan and ambrisentan), phosphodiesterase (PDE)-5 inhibitors (sildenafil and tadalafil) and calcium channel blockers (for those responsive to acute vasoreactivity testing).[7] Patients who respond well to acute vasodilator testing during cardiac catherization are good candidates for calcium channel blocker therapy. This usually applies to small subset of patients with IPAH with a sustained response to CCB therapy (functional class I or II with normal or near-normal hemodynamics after several months of treatment). Long-acting nifedipine or diltiazem or amlodipine are recommended. Of the treatments for PAH, epoprostenol is the only agent that has been shown to decrease mortality, improve exercise capacity and improve hemodynamic measures.[7] The PDE-5 inhibitors and ERA antagonists have been shown to decrease hospitalizations, improve exercise capacity and improve hemodynamic measures.[12] Before the approval of riociguat, there were no approved medical therapies for CTEPH. The standard treatment for CTEPH is pulmonary endarterectomy, which can be curative. Atrial septostomy or lung transplantation is an option for advanced PAH, unresponsive to other treatments.[7,12] Bosentan has been studied in patients with CTEPH, demonstrating an increase of 36 m in 6MW distance after 3-6 months (95% CI, 33.6 to 38.2; $p<0.001$).[17]

Methods:

A Medline literature search ending in May 2014 for new systematic reviews and randomized controlled trials (RCTs) for PAH treatments was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, the following were reviewed: one treatment guideline[7], four systematic reviews[12,14,18,19] and six RCTs.[1-6]

Systematic Reviews:

AHRQ – Pulmonary Arterial Hypertension: Screening, Management and Treatment[12]

AHRQ recently conducted a comparative effectiveness review for PAH. The focus of the review was to update new data on combination therapies and treatments for PAH. Included studies were assessed for quality and graded using the Cochrane Risk of Bias tool. More than 3,600 patients were studied in 28 randomized, controlled trials (96% were rated good or fair quality). The review included the following treatments: bosentan, sildenafil, iloprost, epoprostenol, tadalafil, ambrisentan, treprostinil and vardenafil. The analysis found that there was low strength of evidence that patients on monotherapy benefited more from combination therapy instead of continuing monotherapy. There was limited evidence that prostanoids provided a mortality benefit (low strength of evidence). There was insufficient evidence to draw mortality conclusions with the ERAs and PDE-5 inhibitors. There was moderate strength of evidence that

ERAs, PDE-5 inhibitors and prostanoids improved 6MW distance. Hospitalizations were reduced with ERAs and PDE-5 inhibitors (moderate strength of evidence). All classes improved hemodynamic measures, however, clinical significance of these measures still needs to be delineated.

COCHRANE – Endothelin Receptor Antagonists for Pulmonary Arterial Hypertension (Review)[18]

A systematic review was done to analyze the efficacy of ERAs for PAH. Twelve double-blind, placebo-controlled, randomized controlled trials lasting 12 weeks to 6 months studying bosentan, sitaxsentan (removed from the market due to hepatic toxicity) and ambrisentan were included. A total of 1471 patients with predominately idiopathic PAH and WHO functional class II and III were studied. Eleven of the studies were placebo controlled trials and one study compared bosentan to sildenafil. Average improvement in the 6MW distance was 33.71 meters (95% CI 24.90 to 42.52meters) compared to placebo. Statistically significant improvements in functional class were found and there was a trend toward a mortality benefit. There was no significant difference found between bosentan and sildenafil, however, small sample size in the study limits the ability to draw strong conclusions. ERAs were well tolerated and there was a low occurrence of hepatic toxicity.

CADTH – Drugs for Pulmonary Arterial Hypertension: A Systematic Review of Clinical-Effectiveness of Combination Therapy[19]

A 2009 Canadian Agency for Drugs and Technologies in Health performed a systematic review on the use of combination treatment for idiopathic PAH. Four studies lasting 12 weeks to 6 months and two guidelines were included. Combinations studied were; sildenafil and epoprostenol, inhaled iloprost and bosentan, bosentan and epoprostenol and bosentan and sildenafil. Combination therapy demonstrated a benefit in 6MWdistance (treatment difference of 26 to 28.8 m). Due to limited evidence, guidelines recommend combination therapy be reserved for patients failing monotherapy, those with severe disease and as part of a clinical trial.

Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension[14]

Barst, et al, reviewed PAH trials and graded the evidence to support a treatment algorithm. Recommendations were based on the quality of the evidence and the net benefit of therapy. Calcium channel blockers were moderately recommended for patients in WHO Class I-IV who are responsive to acute vasoreactivity testing. Ambrisentan, bosentan, and sildenafil are strongly recommended for patients in WHO Class II and these same agents, in addition to IV epoprostenol and iloprost inhalation, are strongly recommended for patients in WHO Class III. Tadalafil, SQ treprostinil and sitaxsentan (no longer available) are moderately recommended for patients in WHO Class III. Epoprostenol IV is strongly recommended for patients in WHO Class IV patients based on evidence of a survival benefit. Inhaled iloprost is moderately recommended for WHO class IV patients. Iloprost IV and treprostinil IV are moderately recommended based on expert opinion. Combination therapy is appropriate for patients who remain in WHO Class III despite monotherapy. Atrial septostomy and lung transplantation are an option for patients who fail to respond to medical treatments.

New Guidelines:

ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension[7]

The ACCF/AHA Consensus document recommends an evidence-based treatment algorithm for the management of PAH. Recommendations are based on available studies and expert opinion. Therapies included are; background therapies (anticoagulation, diuretics, oxygen and digoxin), calcium channel blockers, epoprostenol, treprostinil, iloprost, bosentan, sitaxsentan, ambrisentan, and sildenafil (tadalafil, macitentan and riociguat not approved at time of guideline publication). General recommendations include warfarin for anticoagulation, diuretics for patients with right ventricular (RV) volume overload and oxygen if needed to maintain saturations above 90%. Calcium channel blockers should be given to appropriate patients, based on acute vasodilator testing. Patients that are considered lower risk should be offered oral ERA or PDE-5 inhibitor therapy. High risk patients should be given an IV prostacyclin first line. Critically ill patients should be given IV epoprostenol based on evidence of improved exercise capacity, hemodynamics and survival benefit. ERAs or PDE-5 inhibitors are

appropriate for patients at lower risk (functional class II or III). Both ERAs and PDE-5 inhibitors have been shown to improve exercise capacity in patients with PAH. Combination therapy may be an option for PAH patients not responding to monotherapy. Lung transplantation and/or atrial septostomy can be considered for those patients who fail medical management.

ACCP – Updated Treatment Algorithm of Pulmonary Arterial Hypertension[20]

Recommendations from the most recent World Symposium on Pulmonary Hypertension (WSPH) are summarized in this update. Evidence was graded using the European Society of Cardiology grades of recommendations (Class I- recommended; Class II- conflicting evidence regarding usefulness; Class IIa – should be considered; Class IIb – may be considered; Class III – not recommended). Levels of evidence were also incorporated (level A to level C; A being the strongest). Supportive therapy with anticoagulants, diuretics, oxygen and digoxin should be considered for patients with PAH. Pharmacotherapy recommendations are based on available evidence and WHO functional class. PAH specific treatment is indicated in those unresponsive to vasodilatory testing or those not responding to calcium channel blocker therapy. For patients with WHO-FC II symptoms the following therapies are considered recommended based on a level A or B recommendation; ambrisentan, bosentan, macitentan, riociguat, sildenafil, and tadalafil. Ambrisentan, bosentan, epoprostenol IV, iloprost inhaled, macitentan, riociguat, sildenafil, tadalafil, and treprostinil s.c. and inhaled are recommended for patients with WHO-FC III patients (Class I; evidence level A and B). Class IIa, evidence C recommendations for WHO-FC III patients are iloprost IV and treprostinil IV and beraprost is recommended for these same patients based on a Class IIb, evidence level B. Lastly, combination therapy can be considered in WHO-FC III patients (Class IIb; evidence level C). Survival benefit have been demonstrated with IV epoprostenol and should be first-line therapy for WHO-FC IV patients (Class I; evidence level A or B). Ambrisentan, bosentan, iloprost inhaled/IV, macitentan, riociguat, sildenafil, tadalafil and treprostinil SC/IV/inhaled are alternatives for WHO-FC IV patients (Class IIa; evidence level C). Initial combination therapy can also be considered for patients with WHO-FC IV symptoms (Class IIb; evidence level C). Patients experiencing an inadequate response to combination therapy should be considered for lung transplantation.

New Primary Literature:

New Drug Evaluation- Riociguat (Adempas®)

FDA Indications[21]:

Riociguat is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class or PAH (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

Clinical Efficacy Data (see evidence table below) [1,2]:

Riociguat has been studied in two, phase III trials for FDA approval. PATENT-1 was in patients with WHO group I PAH and the second study was CHEST-1, which included patients in WHO group 4 PAH. The primary outcome measure was the change from baseline to the end of week 12 in the 6MW distance in PATENT-1 and 16 weeks in CHEST-1.

Pulmonary Arterial Hypertension

In the fair-good PATENT-1 study, 443 patients were randomized to receive riociguat titrated to a maximum of 2.5 mg three times daily (R2.5), riociguat titrated to a maximum of 1.5 mg three time daily (exploratory only, not included in the efficacy analysis) or placebo in patients with symptomatic PAH for 12 weeks. Patients were eligible is they had a pulmonary vascular resistance >300 dyn·sec·cm^{-5}, a mean pulmonary-artery pressure of at least 25 mm Hg and a baseline 6-

minute walk distance of 150 to 450 m. Patients were allowed to take ERAs or prostanoids (excluding IV prostanoids) at doses that had been stable for at least 90 days. The majority of patients were white females with and the average age of 51 years and PAH WHO functional class II or III. Fifty percent of patients were receiving other treatments for PAH (44% ERAs and 6% prostanoids). For the primary endpoint, the 6MW distance increased 30 m in the R2.5 group compared to 6 m in the placebo group (lease square mean difference [LSMD] 36 m, 95% CI 20 to 52, p<0.001). The change from baseline in the 1.5 mg maximum dose group was similar to the 2.5 mg group with a 6 MWD of 31 m. There were more patients in the 1.5 mg group who moved to a lower functional class compared to the 2.5 mg group, 24% (ARR 10%, NNT 10) and 21% (ARR 7%, NNT 14), respectively. Patient with WHO functional class III and IV and on background prostanoids received the most benefit from riociguat therapy. Efficacy results were similar for patients on other treatments for PAH and for those only on riociguat and for treatment naïve patients. PATENT-2 is an ongoing extension trial, including eligible patients from PATENT-1. An unpublished interim analysis showed a further increase in 6MW distance during the first 12 weeks.

In PATENT-1 there were 9% more patients with WHO functional class III PAH in the R2.5 group compared to placebo. This could favor the efficacy results of R2.5, being that this group received the most benefit from treatment. Data from ongoing extension studies will be helpful to determine efficacy beyond 12-16 weeks. Additional studies are needed to determine the comparative effectiveness to other PAH therapies.

Chronic Thromboembolic Pulmonary Hypertension

In the good quality CHEST-1 trial, patients were randomized in a 1:2 ratio to riociguat 0.5 – 2.5 mg three times daily (R) or placebo for 16 weeks. Two hundred sixty one patients with inoperable chronic thromboembolic PAH or persistent or recurrent PAH after pulmonary endarterectomy were studied for 16 weeks. Patients on background PAH treatment within three months of study initiation were excluded. The mean age was 59 years and the majority (66%) of patients were female. At week 16, 77% of patients enrolled were taking riociguat 2.5 mg three times daily. The primary endpoint was significantly improved in patients taking riociguat over placebo (LSMD 46m; 95% CI 25 to 67, p<0.001). Riociguat significantly improved WHO functional class compared to placebo (ARR 18%, NNT 6). Patients in WHO functional class 3 or 4 had a better response in the 6MW distance than those in class 1 or 2, LSMD 54 (95% CI 28 to 79) and 24 (95% CI -14 to 63), respectively. Patients in the postoperative CTEPH subgroup were shown to not have a significant benefit from treatment (LSMD 26, 95% CI -16 to 68). Improvement in functional class was significantly improved compared to placebo, 33% vs. 15%, respectively.

Clinical Safety (see evidence table below)[1,2]:

Withdrawals due to adverse events were low (3%) in both studies. Adverse events seen in ≥10% of patients in the riociguat group were headache, dyspepsia, peripheral edema, nausea, dizziness, diarrhea, vomiting, nasopharyngitis, and hypotension. The most common serious reactions were syncope, worsening PAH, chest pain, right ventricular failure and hemoptysis. The following rare, but serious adverse events were associated with riociguat; increased hepatic enzymes, acute renal failure, syncope, esophageal pain and swelling, supraventricular tachycardia and right ventricular failure. Dose-dependent decreases in blood pressure and hypotension are concerns when riociguat is used in a non-study setting.

Additional data on mortality and long-term studies would be helpful in defining the role of riociguat in patients with Group 4 PAH.

Conclusion

There is moderate strength of evidence that riociguat improved 6MW distance in patients in with CTEPH (WHO Group 4). There was low to moderate strength of evidence that riociguat improved the 6MW distance in patients with PAH (WHO Group 1). Changes in 6MW distance ranged from 33 to 39 m, which is at the lower end of clinically significant improvement and consistent with PDE-5 inhibitors which work by a similar mechanism of action. Adverse events, such as syncope and hypotension, are similar to other vasodilators. Interim analyses of long term extension studies (PATENT-2 and CHEST-2 ongoing) suggest

persistence of effect up to 9 months. It has been suggested that the efficacy of riociguat would be superior to PDE-5 inhibitors, due to the lack of dependence of riociguat on nitric oxide concentrations, which can be reduced in PAH. There are no head to head studies to validate this assumption at this time.

New Drug Evaluation- Macitentan (Opsumit®)

FDA Indication[22]:

Macitentan is an ERA indicated for the treatment of PAH (WHO Group 1) to delay disease progression. Macitentan is a structural modification of the ERA, bosentan. Macitentan affinity for endothelin receptors and time of receptor occupancy is greater than other ERAs but clinical significance of this is unknown.

Clinical Efficacy Data (see evidence table below)[3]:

Macitentan was studied in one, phase III, good quality trial (SERAPHIN) lasting an average of 96 weeks. Patients (N=742) with idiopathic or heritable PAH, whom were predominately female and average age of 46 years, were randomized to macitentan 3 mg daily, 10 mg daily or placebo. Most patients had functional class II or III PAH and 60% were on background PAH therapy (excluding subcutaneous and intravenous prostanoids and ERAs). The primary outcome was the time from initiation of treatment to the first occurrence of the composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with subcutaneous or intravenous prostanoids, or worsening PAH (decreased 6MW distance, worsened PAH symptoms, and need for additional PAH treatment). The composite primary endpoint occurred in 31.4%, 38.0% and 46.4% of patients in the macitentan 10mg, macitentan 3mg and placebo groups, respectively. Macitentan 10 mg was found to be significantly better than placebo (HR 0.55, 95% CI 0.39 to 0.76, $p<0.001$), where the 3 mg dose was not. The most common primary endpoint event was worsening PAH. The change in 6MWD was modest with most benefit seen in the macitentan 10 mg group, followed by macitentan 3 mg and a decrease in the placebo group, 12.5 m, 7.4 m, and -9.4 m, respectively. Mortality rates were not significantly different between groups for macitentan 3 mg, macitentan 10 mg and placebo, 8.4%, 5.8% 7.6%, respectively (study underpowered to show effect on mortality alone). Macitentan efficacy was consistent with the 10mg dose in patients with or without background PAH therapy and irrespective of etiology for the primary endpoint. Subgroup analysis showed macitentan 10 mg to be statistically significantly better than placebo in patients on background therapy for the change in 6MWD and for patients with WHO functional class III/IV symptoms. In North American study sites, macitentan treatment was not statistically different from placebo.[23]

Clinical Safety Data (see evidence table below):

The most common side effect seen in the study with macitentan was anemia, headache and nasopharyngitis.[3] In general ERAs are linked to increased LFT elevations. Macitentan has only weakly been associated with this adverse effect but continued monitoring and surveillance is recommended due to the small study population and limited trial experience.[22] Discontinuations due to adverse events were low, 12.4%, 13.6% and 10.7% in the placebo, macitentan 3mg and macitentan 10mg group, respectively.[3] Serious adverse effects were lower in the macitentan 3 mg and macitentan 10 mg group compared to placebo, 52%, 45% and 55%, respectively.

Conclusion:

There is moderate strength of evidence that macitentan 10mg improves morbidity in patients with PAH based on one small study lasting approximately 2 years. Only modest efficacy was demonstrated in the change in 6MWD. Common adverse events are anemia, headache and nasopharyngitis. Study design limitations include lack of details on blinding, treatment allocation concealment, and randomization.

New Drug Formulation - Treprostinil (Orenitram®)

FDA Indication[24]: Oral treprostinil is indicated for the treatment of PAH (WHO Group I) to improve exercise capacity. Study data was mostly conducted in patients with WHO functional class II-III symptoms and with idiopathic or heritable forms of PAH or PAH associated with connective tissue disease. Use of oral

treprostinil as monotherapy showed small exercise benefits. Studies with oral treprostinil in combination with other vasodilator therapy produced no additional benefit.

Clinical Efficacy Data (see evidence table below) [4,5,6]

The oral form of treprostinil was studied in three, phase III, PC, randomized-controlled trials. In two trials (FREEDOM-C and FREEDOM-C2) treprostinil was combined with ERAs and/or PDE-5 inhibitors. In these trials no additional benefit of adding oral treprostinil was found. In the third study, FREEDOM-M, treprostinil 1mg twice daily (titrated to clinical efficacy) was compared to placebo in 349 patients for 12 weeks. Patients were predominantly female with an average 6MW distance of 329m. Patients were allowed to continue on conventional PAH treatments but prostacyclins, ERAs and PDE-5 inhibitor use was prohibited. The primary endpoint was change in 6MW distance at 12 weeks. The median difference in favor of treprostinil was 26m (95%CI, 10.0 to 41.0, p= 0.0001) in the ITT population. The combined 6MWD/Borg score at weeks 4, 8 and 12 was the only significantly improved secondary outcome in the ITT population.

Clinical Safety Data (see evidence table below):

The most common adverse events seen in clinical trials were nausea, headache and diarrhea. Severe adverse seen in trials were right ventricular failure, dyspnea, lower respiratory tract infection and worsening PAH. Discontinuations due to adverse events were higher in the treprostinil group compared to placebo. Studies that had lower strength tablets (0.25mg) available for initiation and titration resulted in better tolerability and efficacy.

Conclusion:

There is low strength of evidence that oral treprostinil improves exercise capacity in patients with PAH. There is moderate strength of evidence that treprostinil added no additional benefit to ERAs and/or PDE-5 inhibitor therapy when used in combination. Adverse events were common with treprostinil therapy and led to treatment discontinuation in 10-14% of patients.

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:

1.) Exercise tolerance
2.) Disease progression
3.) Mortality

Study Endpoints:

1.) Change from baseline in 6MW distance
2.) Change in WHO functional class
3.) Composite endpoint of death, atrial septostomy, lung transplantation, initiation of SQ/IV prostanoids or worsening PAH

Evidence Table

PATENT-1[1]

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Ghofrani, et al Phase III, RCT, DB, PC 30 Countries	1. Riociguat up to 2.5 mg three times daily (R2.5) 2. Riociguat up to 1.5 mg three times daily (R 1.5)* 3. Placebo QD (P) * Included for exploratory purposes; not included in the efficacy analysis	Mean Age: 51 Female: 79% Baseline 6-Min walk distance(m): 368±69 **Inclusion**: Patients 18-80 years old with symptomatic Group I PAH if pulmonary vascular resistance was >300 dyn·sec·cm^{-5}, a mean pulmonary- artery pressure of at least 25 mm Hg and a 6-minute walk distance of 150 to 450 m and if on no other PAH treatment or endothelin-receptor antagonist or prostanoids at stable doses for 90 days. **Exclusion**: Patients taking intravenous prostanoids or phosphodiesterase type 5 inhibitors, history of pulmonary or cardiac disease, pregnancy, PAH associated with HIV, schistosomiasis and chronic hemolytic anemia.	1. 254 2. 63 3. 126	12 weeks	Change from baseline at week 12 (m): R2.5:+30 R1.5: +31.1 P: -6 LSMD (R2.5 vs. P): 36 (95% CI, 20 to 52, p<0.001) LSMD (R1.5 vs. P): 37.35 (95% CI, 12 to 63, p<0.001) Improvement in WHO functional class: R2.5: 53 (21%) R1.5: (24%) P: 18 (14%) P=0.003 (R2.5 vs. P) RR: 1.5 (R2.5 vs P) RR: 1.7 (R1.5 vs P) Clinical Worsening: R2.5: 8 (6%) P: 3 (1%) P= 0.005 Borg Dyspnea Score: R2.5: -0.4 P: 0.1 P=0.002	NA R2.5 vs P ARR: 7 NNT: 14 R1.5 vs P ARR: 10% NNT: 10 ARR: 5 NNT: 20 NA	Serious Adverse Events: R2.5: 8 (3%) R1.5: 2 (3.25%) P: 5 (4%) Withdrawal due to Adverse Events: R2.5: 8 (3%) R1.5: 1 (1.6%) P: 9 (7%)	NA NA	**Quality Rating: Fair-Good** **Internal Validity: RofB** Selection: Patient randomized and allocation concealment done using a computer-generated random code and interactive voice response system. Groups similar at baseline. Performance: Double-blind treatment design. Patients and investigators were blinded. Sham dosage adjustments using IVR system based on blood pressure done to maintain blinding. Detection: Sponsor and contract research personnel blinded. Unclear on outcome assessors. Attrition: mITT analysis was used with LOCF for missing data. Overall 7-12% discontinued treatment prior to 12 weeks. **External Validity** Recruitment: recruited from 30 countries. US sites accounted for 6.5% of patients. Patient Characteristics: most patients were white females with idiopathic PAH. Most patients were WHO class II and III. Patients with more severe disease (WHO class III and IV) saw the most benefit from treatment. Fifty percent were on other treatments for PAH. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
CHEST-1[2]									
Ghofrani, et al Phase III, RCT, DB, PC	1. Riociguat 0.5 – 2.5 mg three times daily (R) 2. Placebo (P)	Age: 59 years Female: 66% Baseline 6-Min walk distance(m): 347±80 Inclusion:	1. 173 2. 88	16 weeks	Change from Baseline in 6 MW distance at 16 weeks (m): R: +39 P: -6 LSMD: 46m (95% CI 25 to 67, p<0.001)	NA	Serious Adverse Events: R: 6 (3%) P: 2 (1%) Withdrawal due to	NA	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized via interactive voice response system/interactive web response system and computer generated randomization schedule. Performance: Patient investigators and

26 countries		Patients 18-80 years with inoperable chronic thromboembolic pulmonary hypertension or persistent or recurrent pulmonary hypertension after pulmonary endoarterectomy and pulmonary vascular resistance was >300 dyn·sec·cm^{-5}, a mean pulmonary-artery pressure of at least 25 mm Hg and a 6-minute walk distance of 150 to 450 m. Exclusion: Use of endothelin receptor antagonists, prostacyclin analogues, phosphodiesterase -5 inhibitors or nitric oxide donor within previous 3 months and pulmonary and cardiovascular disease and pregnancy.			Improvement in WHO functional class: R: 57 (33%) P: 13 (15%) P=0.003 Clinical Worsening: R2.5: 4 (2%) P: 5 (6%) P= 0.17 Borg Dyspnea Score: R2.5: -0.8 P: 0.2 P=0.004	ARR: 18 NNT: 6 NS NA	Adverse Events: R: 4 (3%) P: 2 (2%)	NA	sponsor/contract research personnel blinded. Detection: Patient investigators and sponsor/contract research personnel blinded. Unclear on outcome assessors. Attrition: mITT analysis was used with LOCF for missing data. Attrition was low in both groups. **External Validity:** Recruitment: 89 centers in 26 countries. Approximately 6% from US centers. Patient Characteristics: Seventy-seven percent of patients were receiving the maximal riociguat dose (2.5 mg three times daily) at week 16. Most patients had functional class III PAH and inoperable CTEPH. Patients with inoperable CTEPH and higher functional class (III or IV) received the most benefit from treatment. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
SERAPHIN[3]									
Pulido, et al Phase III, DB, PC	1. Macitentan 3 mg daily (M3) 2. . Macitentan 10 mg daily (M10)	Age: 46 years Female: 77% Baseline 6-Min walk distance(m): 360±100.2	1. 250 2. 242	1. 100 weeks 2. 104 weeks	Composite endpoint of death, atrial septostomy, lung transplantation, initiation of SQ/IV prostanoids or worsening PAH : M3: 95 (38%)		Serious Adverse Events: M3: 130 (52%) M10: 109 (45%) P: 137 (55%) Withdrawal due to	NA	**Quality Rating: Good** **Internal Validity: RofB** Selection: Patients were randomized by a central randomization system via interactive voice response or interactive web response. Performance: double-blind treatment design was

39 countries	3. Placebo (P)	Inclusion: Patients 12 years and older with idiopathic or heritable PAH, confirmed PAH by right hear catheterization, 6 MW distance of ≥50 m, class II, III or IV WHO functional class. PAH medications not mentioned below were allowed. Exclusion: Use of endothelin-receptor antagonists, intravenous or subcutaneous prostanoids.	3. 250	3. 85 weeks	M10: 76 (31.4%) P: 116 (46.4%) HR M3 vs. P : 0.70 (95% CI 0.52 to 0.96, P=0.011*) HR M10 vs. P: 0.55 (95% CI 0.39 to 0.76, p<0.001) * Overall alpha set at p=0.01 Death from any cause: M3: 21 (8.4) M10: 16 (6.6) P: 17 (6.8) Change from Baseline in 6 MW distance at 6 months: M3: 7.4 m P: -9.4 m P=0.01 M10: 12.5 m P: -9.4 m P=0.008 Improvement in WHO functional class from baseline to month 6: M3: 20% P: 13% P=0.04 M10: 22% P: 13% P=0.006 Hospitalizations for PAH: M3: 56 (22) M10: 45 (19) P: 79 (32)	 NA M10 ARR: 15 NNT: 7 NA NA NA M10 ARR: 9 NNT: 11 NA	Adverse Events: M3: 34 (13.6%) M10: 26 (10.7%) P: 31 (12.4%)	NA	stated with matching treatment and placebo and identical medication kits. Detection: results were adjudicated by blinded clinical event committee. Attrition: ITT analysis with LOCF was used for data analysis. A total of 13% of patients discontinued the study early. **External Validity:** Recruitment: from 159 centers in 39 countries. Patient Characteristics: Most patients (77%) were female and had predominantly WHO functional class II or III PAH. Over 60% of patients were on background treatments for PAH. Outcomes: event-driven study using morbidity and mortality endpoint. Composite endpoint can exaggerate treatment effect.

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FREEDOM-C[5]									
Tapson, et al Phase III, DB, PC, RCT 72 centers	1. Treprostinil 1mg twice daily (starting dose) [T] 2. Placebo (P) * Treatment given in combination with a PDE-5 inhibitor and/or an ERA	Age: 50 years Female: 82% Mean baseline 6-Min walk distance(m): 346 <u>Inclusion:</u> Patients 12-70 years with symptomatic idiopathic PAH, familial PAH, PAH associated with congenital heart disease, connective tissue disease or HIV, a 6 MW distance of 100 to 450m, stable use of PDE-5 inhibitor and/or ERA therapy within 90 days of study. <u>Exclusion:</u> Pregnancy, nursing, investigational therapy use and other PAH diseases not mentioned in inclusion.	1. 174 2. 176	16 weeks	<u>Median change from Baseline in 6 MW distance at 16 weeks (m):</u> T: 14.5 P: 4.8 (median difference 11m, 95%CI 0.0 to 22.0, P= 0.07) <u>Improvement in WHO functional class:</u> T: 31 (18%) P: 26 (15%) P= 0.94 <u>Clinical Worsening:</u> T: 8 (5%) P: 12 (7%) P = 0.49 <u>Borg Dyspnea Score:</u> T: -0.03 P: 0.38 P= 0.07	N/A N/A N/A N/A	<u>Any Adverse Event:</u> T: 173 (99%) P: 157 (90%) <u>Withdrawal due to Adverse Events:</u> T: 25 (14%) P: 8 (5%)	NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients randomization details were not disclosed. Performance: Study was double-blind with no details on blinding of care providers. Detection: No details on the blinding of outcome assessors were provided. Attrition: mITT analysis was used but methodology for missing data imputation was not provided. Attrition was 22% in the treprostinil group and 14% in the placebo group. **External Validity:** Recruitment: 72 centers in 14 countries. Patient Characteristics: Majority (76%) of patients had WHO functional class III symptoms. Thirty percent of patients were receiving concomitant ERA therapy and 25% were receiving concomitant PDE-5 inhibitor and 45% were taking both. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
FREEDOM-M[4]									
Jing, et al Phase III, DB, PC, RCT 81 centers	1. Treprostinil 1mg twice daily (T)* 2. Placebo (P) * Changed to initiation dose of treprostinil 0.5mg twice daily and then later to	Age: 41 years Female: 75% Mean baseline 6-Min walk distance(m): 329 <u>Inclusion:</u> Patients 12-75 years with idiopathic PAH, hereditary PAH,	1.233 2.116	12 weeks	<u>Change from Baseline in 6 MW distance at 12 weeks (m) for ITT population:</u> T: 26 P: 0 (median difference 26m, 95%CI 10.0 to 41.0, P= 0.0001) <u>Clinical Worsening for ITT</u>	NA	<u>Serious Adverse Events:</u> T: 41 (18%) P: 26 (22%) <u>Withdrawal due to Adverse Events:</u> T: 23 (10%) P: 3 (3%)	NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients randomization details were not disclosed. Performance: Study was double-blind with no details on blinding of care providers. Detection: No details on the blinding of outcome assessors were provided. Attrition: ITT and mITT analysis was used with LOCF applied to missing data. Attrition was 23% in the treprostinil group and 16% in the placebo group.

	0.25mg twice daily	PAH associated with congenital heart disease, connective tissue disease or HIV, a 6 MW distance of 100 to 450m, and stable use of convention PAH therapies. Exclusion: Use of PDE-5 inhibitors, ERAs or prostacyclin therap within 30 days, significant left-sided heart disease or parenchymal lung disease.			population: T: 22 (9%) P: 15 (13%) Death for ITT population: T: 13 (6%) P: 8 (7%) Hospitalization/new therapy for ITT population: T: 9 (4%) P: 5 (4%)	N/A N/A N/A			**External Validity:** Recruitment: Patients were from 81 centers in 7 countries. Patient Characteristics: Majority (61%) of patients had WHO functional class III symptoms. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.
FREEDOM-C2[6]									
Tapson, et al Phase III, DB, PC, RCT 94 centers	1. Treprostinil 0.25mg twice daily* (T) 2. Placebo (P) * Dose was titrated if clinically indicated	Age: 51 years Female: 78% Mean baseline 6-Min walk distance(m): 333 Inclusion: Patients 18-75 years with idiopathic PAH, familial PAH, PAH associated with congenital heart disease, connective tissue disease or HIV, a mean pulmonary- artery pressure of at least 25 mm Hg, a pulmonary capillary wedge pressure or left ventricular end-diastolic pressure o ≤15 mm Hg, pulmonary vascular	1.157 2.153	16 weeks	Placebo adjusted change from Baseline in 6 MW distance at 16 weeks (m): Median difference between T and P: 10 m (95% CI, -2.0 to 22.0, P=0.89) Clinical Worsening: T: 11 (7%) P: 10 (7%)	NA N/A	Any Adverse Event: T: 157 (100%) P: 136 (89%) Withdrawal due to Adverse Events: T: 23 (10%) P: 3 (3%)	NA NA	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients randomization details were not disclosed. Performance: Study was double-blind with no details on blinding of care providers. Detection: No details on the blinding of outcome assessors were provided. Attrition: analysis was used with LOCF applied to missing data. Attrition was 23% in the treprostinil group and 16% in the placebo group. **External Validity:** Recruitment: Patients were from 94 centers. Patient Characteristics: Majority (73%) of patients had WHO functional class III symptoms. The mean dose of treprostinil was 3.1mg twice daily. Newly diagnosed patients received the most improved 6MW distance. Outcomes: The accepted surrogate outcome of 6MW distance was used to evaluate efficacy.

		resistance >3 Wood units and the absence of unrepaired congenital heart disease, use of ERA or PDE-5 inhibitors ≥90 days and stable doses for ≥30 days and baseline 6MW distance of 150-425 m. <u>Exclusion:</u> Pregnancy, nursing, left-sided heart disease or significant parenchymal lung disease, FEV1/FVC ratio <50%, use of investigation medication or change of PAH medication within 14 days.							

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group
[2]**Results abbreviations**: HR = Hazard Ratio, ARR = absolute risk reduction, LSMD= least square mean difference
NNT = number needed to treat, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
Clinical Abbreviations: PAH = pulmonary arterial hypertension, WHO= World Heath Organization

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Appendix 1: Drug Information

NDE: Riociguat (Adempas®)[19]

Pharmacology: Riociguat is a soluble guanylate cyclase inhibitor (sGC) stimulator, an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). Riociguat is proposed to work by sensitizing sGC to endogenous NO and by stimulating sGC by binding to a site independent of NO.

Table 1. Pharmacokinetics[19]

Parameter	Riociguat	Parameter	Riociguat
Half-Life	7-12 Hours	**Renal Dose Adjustment**	Safety and efficacy has not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis.
Elimination	40% renal and 53% hepatic		
Metabolism	CYP1A1,CYP3A, CYP2C8, CYP2J2	**Hepatic Dose Adjustment**	Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child-Pugh class C).

Contraindications/Warnings:

- **Black box warning:** Riociguat should not be given to pregnant females because it may cause fetal harm. Females must acquire riociguat through a REMs program and be using adequate contraception.
- **Contraindications:** Riociguat is contraindicated in pregnancy, use with nitrates or nitric oxide donors in any form, and use with phosphodiesterase inhibitors.
- **Warning:** Caution should be used when prescribing riociguat in patients with symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease. Dose titration should be done cautiously due to varying inter-patient concentrations.

Dose

The recommended dose of riociguat is a starting dose of 1 mg taken three times daily. For patients who can not tolerate the hypotensive effects, the dose should be administered at 0.5 mg three times daily. If systolic blood pressure remains above 95 mmHg and the patient has no signs or symptoms of hypotension, up titrate the dose by 0.5 mg three times a day. Dose increases should be no sooner then 2 weeks apart. If tolerated the dose may be increased to 2.5 mg, three times a day. Intra-patient variability of drug concentrations and metabolism requires individualized dose titration. Dose may need to be adjusted when riociguat is given with CYP3A4 inhibitors/inducers and in patients who smoke.

NDE: Macitentan (Opsumit®)[20]

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Pharmacology: Macitentan is an ERA antagonist that prevents binding of endothelin (ET)-1 to its receptors. This prevents harmful effects of ET-1, such as vasoconstriction, fibrosis, proliferation, hypertrophy and inflammation seen in PAH where the ET system is up regulated.

Table 2. Pharmacokinetics[20]

Parameter	Macitentan	Parameter	Macitentan
Half-Life	16 hours and 48 hours (active metabolite)	**Renal Dose Adjustment**	None recommended
Elimination	50% renal and 24% hepatic		
Metabolism	CYP3A4 and CYP2C19	**Hepatic Dose Adjustment**	None recommended

Contraindications/Warnings:

- **Black box warning:** Macitentan may cause fetal harm and should not be given to pregnant females.
- **Contraindications:** Macitentan should not be used in pregnant females.
- **Warning:** Liver enzymes should be monitored, as other ERAs have been shown to cause hepatotoxicity. Macitentan may cause decreases in hemoglobin and pulmonary edema in patients with pulmonary veno-occlusive disease (discontinue treatment if confirmed). ERAs have been shown to cause decreases in sperm count.

Dose

The recommended dose is macitentan 10mg orally once daily.

New Drug Formulation: Treprostinil (Orenitram®)[22]

Pharmacology: Oral treprostinil is a prostacyclin vasodilator indicated for PAH Group 1 to improve exercise capacity.

Table 3. Pharmacokinetics[22]

Parameter	Treprostinil	Parameter	Treprostinil
Half-Life	Dose-proportional	**Renal Dose Adjustment**	None recommended
Elimination	Oxidation, renal (0.19%) and hepatic (1.3%)		
Metabolism	CYP2C8 and CYP2C9	**Hepatic Dose Adjustment**	Mild impairment initiate treprostinil at 0.125mg dose twice daily and increase every 3-4 days. Avoid use in moderate hepatic impairment and use is contraindicated in severe hepatic impairment.

Contraindications/Warnings:

- **Contraindications:** Severe hepatic impairment (Child Pugh Class C).
- **Warning:** Do not discontinue abruptly, increased risk of bleeding especially if receiving anticoagulants, do not take with alcohol and potential for tablets to be lodged in diverticulum in patients with diverticulosis.

Dose

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The recommended starting dose for treprostinil is 0.25mg twice daily with food. Dose may be increased by 0.25-0.5mg twice daily every 3-4 days to achieve optimal clinical response. Maximum doses in clinical studies were 12-21 mg twice daily. Avoid abrupt discontinuation.

APPENDIX 2:
Suggested PA Criteria

Oral/Inhalation Pulmonary Arterial Hypertension Agents

Goal(s): Approve therapy for covered diagnoses which are supported by the medical literature.
- Erectile dysfunction is not covered by OHP

Length of Authorization:
Up to 12 months

Requires PA:
- Non-preferred drugs

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What is the diagnosis?	Record ICD10 code**.**	
2. Is this an OHP covered diagnosis?	**Yes:** Go to #3	**No**: Pass to RPH. Deny, (Not covered by the OHP)
3. Does the patient have a diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH)?	**Yes:** Go to #8	**No:** Go to #4.

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4. Does the patient have a diagnosis of WHO Group 4 PAH?	**Yes**: Go to #5	**No:** Pass to RPH. Deny (Medical Appropriateness)
5. Is the request for riociguat (Adempas®)?	**Yes**: Go to #6	**No:** Pass to RPH. Deny (Medical Appropriateness)
6. Is the drug being prescribed by a pulmonologist or cardiologist?	**Yes**: Go to #7	**No:** Pass to RPH. Deny (Medical Appropriateness)
7. 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)
8. Will the prescriber consider a change to a preferred product?	**Yes**: Inform provider of alternatives in class.	**No**: Go to #9
9. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Go to #10	**No:** Pass to RPH. Deny (Medical Appropriateness)
10. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 12 months.	**No:** Go to #11

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11. RPH Only: Is the diagnosis above the line and has the clinic provided supporting literature for use?	**Yes:** Approve for length of treatment.	**No:** Deny (not covered by the OHP)

WHO Functional Classification of Pulmonary Hypertension*

Class I—
- Patients with pulmonary hypertension but without resulting limitation of physical activity.
- Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or syncope.

Class II—
- Patients with pulmonary hypertension resulting in slight limitation of physical activity.
- They are comfortable at rest.
- Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or syncope.

Class III—
- Patients with pulmonary hypertension resulting in marked limitation of physical activity.
- They are comfortable at rest.
- Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or syncope.

Class IV—
- Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms.
- These patients manifest signs of right heart failure.
- Dyspnea and/or fatigue may even be present at rest.
- Discomfort is increased by any physical activity.

*Table adapted from "Classification of Pulmonary Hypertension.
" Libby: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed. Peter Libby et al. 2007.web. 21 Oct 2010**.**

DUR Board Action: 7/24/14 (KS), 3/27/14 (KS), 2/23/12 (TW), 9/16/10 (KS)
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Initiated: 1/1/11

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