Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update with New Drug Evaluation: Drugs for Pulmonary Arterial Hypertension

Date of Review: March 2016
Generic Name: selexipag

End Date of Literature Search: November 2015
Brand Name (Manufacturer): Uptravi™ (Actelion Ltd.)
AMCP Dossier Received: yes

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

Purpose for Class Update:
The Oregon Pharmacy & Therapeutics (P&T) Committee previously reviewed the Pulmonary Arterial Hypertension (PAH) drug class in July 2014. Since that time, selexipag was approved as a new drug by the U.S. Food and Drug Administration (FDA) and several agencies have published systematic reviews and clinical practice guidelines that reflect current evidence and best practice.

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 PAH 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 PAH in treatment-naïve patients?
3. Are there specific subpopulations based on disease severity (World Health Organization [WHO] Functional Class [FC]) or other disease characteristics that may benefit more from a specific drug or combination of drugs?

Conclusions:
- The primary outcome studied in most randomized controlled trials (RCTs) was change from baseline in the distance walked in 6 minutes (6-min walk distance, or 6MWD), a measure that may provide some functional information on exercise capacity but does not reliably reflect mortality or clinically relevant morbidity outcomes.[1–3] Details regarding 6MWD are available in the class update but are not reflected in these conclusions.
- Low quality evidence suggests there are no statistically significant differences between monotherapy treatment options for treatment-naïve WHO FC II or III PAH patients with respect to change in WHO FC (worsening or improvement) and composite clinical worsening outcomes.[1] Clinical worsening is generally defined as a composite of time to clinical worsening of PAH (i.e., change in WHO FC), initiation of treatment with intravenous (IV) or subcutaneous (SC) prostanoids, all-cause mortality, heart or lung transplant, or atrial septostomy.[1] The minimal clinically important difference (MCID) between treatments with respect to these study endpoints has not been determined. In addition, the confidence intervals around the calculated risk estimates demonstrate strong imprecision of the evidence and inability to adequately determine differences in efficacy between treatments.

Author: Andrew Gibler, Pharm.D. Date: March 2016

- When low quality evidence was pooled and assessed by drug class, oral prostanoids were the only class not associated with reduced risk for clinical worsening or improvement in WHO FC compared to placebo.[2]
- Low quality evidence also suggests there are no statistically significant differences in mortality between individual PAH monotherapy and placebo as most studies were not sufficiently powered to detect such a difference.[1–3] The exception is parenteral epoprostenol: pooled data from the open-label epoprostenol trials demonstrated a statistically significant, albeit very imprecise, lower risk of mortality compared with placebo (RR 0.33; 95% 0.13 to 0.85).[1] When data were pooled by drug classes offering oral formulations, phosphodiesterase-5 (PDE5) inhibitors were the only drug class associated with mortality reduction (RR 0.22; 95% CI, 0.07 to 0.71; p=0.011).[2]
- There is moderate quality evidence that certain sequential (i.e., add-on) combination therapies may slow clinical worsening compared to monotherapy. However, there is insufficient evidence to guide the duration of initial drug therapy before switching or adding another drug. The addition of tadalafil added to endothelin receptor antagonist (ERA) therapy (mostly bosentan) statistically significantly reduced clinical worsening versus ERA therapy alone (RR 0.39; 95% CI, 0.17 to 0.89), however, the addition of bosentan to sildenafil versus sildenafil alone did not.[4] The addition of macitentan to a PDE-5 inhibitor or prostanoid also statistically significantly reduced risk for clinical worsening (RR 0.74; 95% CI, 0.55 to 0.98) compared to the background therapy alone.[1] However, no sequential combination therapies have shown to be superior to monotherapy when changes in WHO FC (improvement or worsening) are assessed.[1]
- There is also moderate quality evidence that the concomitant initiation of ambrisentan and tadalafil statistically significantly reduces clinical worsening compared to each monotherapy in treatment-naïve patients in WHO FC III (and some WHO FC II) [HR 0.48; 95% CI 0.31-0.72, p<0.001 vs. ambrisentan alone and [HR 0.53; 95% CI 0.34-0.83, p=0.005 vs. tadalafil alone].[5] Evidence is insufficient for other initial combination strategies in treatment-naïve patients.
- There is insufficient evidence to adequately compare the safety profiles between monotherapy treatment options for PAH.[1] Notable treatment-related adverse events (AEs) with a higher incidence than placebo were liver toxicity (bosentan); peripheral edema (riociguat, ambrisentan, bosentan and treprostinil); anemia (macitentan, riociguat and ambristentan); and hypotension (riociguat, epoprostenol and treprostinil).[1] Epoprostenol and treprostinil were frequently associated with nausea, diarrhea, jaw pain, headache and injection-site reactions.[1] When low quality evidence was pooled and assessed by drug class, oral prostanoids were the only drug class associated with significantly more withdrawal events due to adverse events versus placebo.[2]
- There is moderate quality evidence selexipag, a new oral agent recently approved by the FDA, can help reduce complications of PAH in patients in WHO FC II or III.[6] Selexipag does not reduce risk of death due to PAH or from any other cause, but results from one phase 3 trials show selexipag can reduce disease progression, defined as a 15% reduction in 6MWD plus worsening WHO FC or need for additional PAH treatment (6.6% vs. 17.2% with placebo), and hospitalizations for worsening of PAH (13.6% vs. 18.7% with placebo).[6] Adverse events are similar to those seen with prostanoids (headache, jaw pain, nausea and diarrhea).[6]
- There is insufficient evidence to make recommendations for specific subgroups of patients based on disease severity (e.g., WHO FC I or IV) or other disease characteristics who may benefit more from specific drugs or combinations of drugs.[1,7]

Recommendations:

- Continue current prior authorization (PA) criteria for oral/inhaled agents and parenteral agents (Appendix 5).
- Continue to prefer at least one orally dosed endothelin receptor antagonist (ERA) and phosphodiesterase-5 (PDE5) inhibitor without PA.
- Add epoprostenol to the Preferred Drug List (PDL) without PA as a treatment option for patients who require parenteral therapy.
- After review of comparative drug costs in the executive session, no other changes to the PDL were made.

Previous Conclusions:[8]

- There is insufficient evidence to directly compared riociguat to other PAH treatments. There is moderate strength of evidence that riociguat improved the 6MWD in patients with chronic thrombotic/embolic disease and low to moderate evidence in patients with PAH. Changes in 6MWD distance ranged from 33 to 39 meters (m), which is at the lower end of clinically significant improvement and consistent with PDE5 inhibitors, which work by a similar mechanism of action. Adverse events, such as syncope and hypotension, are similar to other vasodilators.
- 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 SC 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 6MWD at 6 months with a treatment effect of 22 m for the macitentan 10 mg group. Patients on background PAH treatment and those with WHO FC III/IV symptoms received the most benefit from treatment. Common adverse events are anemia, headache and nasopharyngitis.
- Studies comparing oral treprostinil to other PAH therapies are lacking. There is low strength of evidence that oral treprostinil improves the 6MWD in patients not on other vasodilatory therapy for PAH compared to placebo, 26 m and 0 m, respectively. Oral treprostinil use in patients taking other PAH therapies demonstrated no significant difference in the 6MWD when compared to placebo. Oral treprostinil was associated with headache, nausea and diarrhea in clinical trials.
- 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.

Previous Recommendations:[8]

- Prior authorize riociguat to ensure appropriate use by qualified providers.
- 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.

Background:

Pulmonary arterial hypertension is a complex, multifactorial chronic disease characterized by progressively elevated pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) that results in high morbidity and early mortality.[1] PAH can affect both males and females of all ethnicities and ages with a prevalence of 12 to 50 cases per million people; however, PAH is most common among females and in people ages between 20 and 40 years.[1] PAH can be categorized into 4 subgroups: idiopathic PAH (IPAH), familial PAH (FPAH), drug-induced PAH, and PAH associated with concurrent medical conditions such as connective tissue disease, HIV infection, portal hypertension, or congenital heart disease.[1] Clinical trials of PAH-specific therapies generally enroll patients under the broader definition of PAH, but enrolled subjects predominantly have had IPAH or PAH associated with systemic sclerosis.[9]

Symptoms suggestive of pulmonary hypertension may include dyspnea upon exertion, fatigue or weakness, angina, syncope, peripheral edema and abdominal distension.[10] The clinical severity of patients with pulmonary hypertension (PH) is classified using WHO FC, which ranges from class I (asymptomatic) to class IV (severe symptoms) (Table 1). Despite its inter-observer variability, the WHO FC is widely used to classify stage of PAH and remains one of the most powerful predictors of survival at diagnosis and at follow-up.[11]

Table 1. WHO Functional Classification of Patients with Pulmonary Hypertension.[10]

Functional Class	
I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

The pathophysiology of PAH involves vasoconstriction, endothelial dysfunction, dysregulated smooth muscle cell growth, inflammation and thrombosis, which contributes to overload of the right heart ventricle and progressive right-sided heart failure.[1] An initial approach to management includes acute vasoreactivity testing with an oral calcium channel blocker (CCB) and supportive care with diuretics (increased fluid retention), digoxin (may improve cardiac output and slow ventricular rate), and anticoagulants (increased risk for venous thromboembolism).[11] Treatment with a CCB (e.g., amlodipine, nifedipine or diltiazem) is important in the few patients who have a favorable response to vasoreactive testing.[11] When warranted, PAH-specific therapy should be initiated in patients without vasoreactivity.[11] These therapies are designed to reverse to some extent the pathophysiology of PAH.[11] PAH-specific therapy belongs to 5 general classes (Table 2). Drug therapy for PAH involves a complex strategy that includes initial evaluation of disease severity and subsequent response to treatment.

Table 2. PAH-specific Drug Therapy.

Endothelin Receptor Antagonists	Phosphodiesterase-5 Inhibitors	Prostanoids (prostacyclin analogs)	Prostacyclin Receptor Agonists	Soluble Guanylate Cyclase Stimulators
• Ambrisentan (oral) • Bosentan (oral) • Macitentan (oral)	• Sildenafil (oral and injectable) • Tadalafil (oral)	• Epoprostenol (injectable) • Iloprost (inhaled) • Treprostinil (oral, inhaled and injectable)	• Selexipag (oral)*	• Riociguat (oral)

* Selexipag is an agonist at the prostacyclin PGI2 receptor, but it is not a prostacyclin analog. It was recently approved by the FDA in December 2015 for use in PAH to delay disease progression and reduce risk for hospitalization for PAH.[12] A new drug evaluation of selexipag is included as part of this drug class update.

Estimated 1-year mortality associated with PAH can be classified into 3 risk categories (Low risk = mortality <5%; Intermediate risk = 5-10%; or High risk = >10%), which is largely dependent on progression of symptoms, WHO FC, 6MWD, echocardiographic and hemodynamic factors.[11] In general, patients who present with non-progressive disease in WHO FC I or II with a 6MWD greater than 440 m and no signs of clinically relevant right ventricular (RV) dysfunction are categorized as low risk.[11] Patients with intermediate risk often present in WHO FC III with moderately impaired exercise capacity and signs of RV dysfunction, but not RV failure.[11] Patients at high risk present in WHO FC III or IV with progressive disease and signs of severe RV dysfunction or with RV failure and secondary organ dysfunction.[11]

Author: Andrew Gibler, Pharm.D. Date: March 2016

Clinical trial outcomes of these agents have been primarily limited to hemodynamic endpoints, exercise capacity (i.e., 6MWD) endpoints, and time to clinical worsening end points. Hemodynamic and echocardiographic measures provide an assessment of cardiac impairment which may be useful when adjusting therapy, but the clinical relevance of these endpoints is difficult to assess and not are consistently helpful when choosing initial drug therapy.[9] The 6MWD endpoint is the most widely used endpoint in trials of drugs for PAH but has been inconsistently correlated with mortality and morbidity outcomes. However, 6MWD can provide some functional information of exercise capacity.[1] Treatment goals proposed for 6MWD, which are limited to selective cohort data and clinical opinion, have ranged from 380 m or greater to 500 m or greater.[11] Clinical worsening is a composite of some clinically relevant endpoints such as mortality and morbidity outcomes.[1] Clinical worsening is generally defined as a composite of time to clinical worsening of PAH (i.e., change in WHO FC), initiation of treatment with IV or SC prostanoids, all-cause mortality, heart or lung transplant, or atrial septostomy.[1]

No FDA-approved therapy has been shown to prevent progression of PAH which remains an incurable disease.[9] Thus, the overall treatment goals for patients with PAH are to slow disease progression, improve morbidity outcomes (i.e., hospitalizations) and slow the high mortality associated with the disease.

Methods:
A Medline literature search for new systematic reviews and 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 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, 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. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Canadian Agency for Drugs and Technologies in Health (2015)[1]
The CADTH conducted a systematic review and meta-analyses to assess the comparative clinical efficacy and safety of PAH drugs used as monotherapy or as sequential combination therapy in adults.[1] The PAH drugs evaluated included oral ERAs (ambrisentan 5 mg and 10 mg once daily, bosentan 125 mg twice daily, macitentan 10 mg once daily), the oral sGC stimulator riociguat 2.5 mg at three times daily, oral PDE5 inhibitors (sildenafil 20 mg three times daily, tadalafil 40 mg once daily), and prostanoids (IV epoprostenol and IV or SC treprostinil).[1] Comparative studies of adults with PAH who received drugs and doses of treatments approved by Health Canada were eligible for inclusion.[1] Inhaled iloprost and oral and inhaled formulations of treprostinil, which are approved by the FDA but not Health Canada, were not included.[1] Of the studies that met inclusion criteria, 18 RCTs compared PAH treatments in treatment-naïve patients (i.e., monotherapy) and 4 RCTs compared sequential combination therapy.[1] Most studies were short-term (12-16 weeks) with small sample sizes (n=60-70). Change in 6MWD from baseline was the primary outcome in most trials. Data for meta-analysis was sufficient for 4 outcomes: clinical worsening, WHO FC improvement, WHO FC worsening and 6MWD.[1] For these outcomes, relative risks (RR) were calculated but raw data from individual studies were not presented. Pre-specified sub-group analyses were performed based on age, baseline WHO FC, baseline 6MWD, gender, background pharmacotherapy, and etiology subtype of PAH (e.g., IPAH, FPAH or other).[1] The methodological approaches to randomization and allocation concealment were generally adequate in most studies, although all 3 epoprostenol studies were open-label.[1] In addition, the intervention groups in the epoprostenol trials had higher baseline 6MWD than those in the placebo

groups (278 m vs. 239 m), suggesting that patients in the placebo group were sicker than those in the epoprostenol groups. It is also important to note that 2 studies of bosentan enrolled patients in the intervention group who had been diagnosed with PAH for much longer than the placebo groups (average 40.4 months vs. 28.0 months). Otherwise, demographic and baseline characteristics in the studies were generally balanced between intervention and comparator groups and reflected those in the general PAH population.[1]

Monotherapy (Treatment-naïve Population)

For clinical worsening, data for meta-analyses were available for macitentan, riociguat, ambrisentan, bosentan, sildenafil, and tadalafil.[1] A statistically significant reduction in risk for clinical worsening versus placebo was found with macitentan (RR 0.59; 95% CI, 0.40 to 0.86), ambristentan 5 mg (RR 0.32; 95% CI, 0.13 to 0.79) and bosentan (RR 0.29; 95% CI, 0.11 to 0.72), but not for riociguat, ambrisentan 10 mg, sildenafil, and tadalafil.[1] Drugs that did not show a statistically significant reduction likely lacked adequate study power since studies had short durations and thus few events. Wide confidence intervals around these results also demonstrate imprecision of these data. There were no statistically significant differences found between these drugs with respect to clinical worsening outcomes.[1] The minimal clinically important difference (MCID) between treatment groups with respect to clinical worsening in these studies has not been determined.[1] Sensitivity analyses did not show marked change in the relative treatment effects.[1]

For WHO FC improvement, data for meta-analyses were available for riociguat, ambrisentan, bosentan, sildenafil, tadalafil, epoprostenol, and treprostinil.[1] Epoprostenol (RR 10.18; 95% CI, 1.91 to 54.24), sildenafil (RR 3.91; 95% CI, 1.55 to 9.88), and tadalafil (RR 2.33; 95% CI, 1.01 to 5.41) showed statistically significant improvement in WHO FC compared with placebo, while riociguat, ambrisentan, bosentan, and treprostinil did not.[1] There were no differences found between the 5 mg and 10 mg doses of ambrisentan and the 1.5 mg and 2.5 mg doses of riociguat for WHO FC improvement.[1] For FC worsening, data for meta-analyses were available for riociguat 2.5 mg, ambrisentan (both doses), bosentan, sildenafil, tadalafil, and epoprostenol; however, statistically significant differences versus placebo were only reached for ambrisentan 5 mg (RR 0.14; 95% CI, 0.04 to 0.45) and 10 mg (RR 0.27; 95% CI, 0.08 to 0.93) and riociguat 2.5 mg (RR 0.24; 95% CI, 0.09 to 0.67).[1] There were no differences found between the 5 mg and 10 mg doses of ambrisentan and the 1.5 mg and 2.5 mg doses of riociguat for FC worsening.[1] Again, the MCIDs of WHO FC improvement and worsening are unclear and sensitivity analyses did not show marked change in the relative treatment effects.[1] The confidence intervals around the calculated risk estimates were very wide, showing imprecision of the evidence and inability to adequately determine differences in efficacy between treatments.

Change in 6MWD from baseline was used as the primary outcome in 14 of the 18 studies even though improvement in 6MWD does not reflect benefit in clinical outcomes, such as all-cause mortality, hospitalization or initiation of PAH rescue therapy.[1] Data for meta-analyses were available for macitentan, riociguat, ambrisentan, bosentan, sildenafil, tadalafil, epoprostenol, and treprostinil.[1] All of the drugs except macitentan, in which 6MWD was studied as a secondary outcome and was not adequately powered, showed statistically significantly increase in 6MWD compared with placebo.[1] Epoprostenol had the largest mean difference (MD 71.7 m), followed by ambrisentan 10 mg (MD 53.2 m), both of which were statistically superior to macitentan and treprostinil.[1] All of the remaining treatments were statistically similar in 6MWD.[1] The MCID for the change in 6MWD from baseline has been estimated to be 33.0 m (range: 25.1 m to 38.6 m).[1] However, sensitivity analyses were not conducted for change in 6MWD since it is a surrogate outcome that has not clearly shown to reflect benefit in clinically relevant outcomes.[1]

Combination Therapy (Treatment-experienced Population)

Several studies of combination therapy were evaluated but did not meet the selection criteria for the review.[1] Data for meta-analysis for clinical worsening, FC improvement, FC worsening and 6MWD were only available for riociguat 2.5 mg 3-times daily and tadalafil 40 mg daily when added to background ERA therapy (mostly bosentan).[1] Tadalafil plus an ERA (RR 0.39; 95% CI, 0.17 to 0.89) but not riociguat 2.5 mg plus and ERA (RR 0.16; 95% CI, 0.02 to 1.50) statistically

significantly reduced clinical worsening versus placebo plus an ERA; however, these combinations were not statistically significantly different from ERA monotherapy when WHO FC improvement or worsening were assessed.[1] The 6MWD also significantly improved with these combinations.[1] Data for meta-analysis for clinical worsening and 6MWD was also available for the addition of macitentan to a PDE-5 inhibitor or prostanoid agent.[1] The combination statistically significantly reduced risk for clinical worsening (RR 0.74; 95% CI, 0.55 to 0.98) and improved 6MWD (RR 25.70; 95% CI, 7.04 to 44.36) compared to the background therapy alone.[1]

Other Efficacy Outcomes

The number of deaths in all studies was relatively low, except in one study of epoprostenol and one study of treprostinil, where 25% and 36% of patients in the placebo groups died, respectively, albeit in patients with more severe disease (WHO FC III or IV).[1] In one epoprostenol trial, there were 8 deaths reported with placebo and none in the intervention group (RR 0.06; 95% CI, 0.00 to 0.96) and the pooled data from the epoprostenol trials demonstrated a statistically significant, albeit very imprecise, lower risk of mortality compared with placebo (RR 0.33; 95% 0.13 to 0.85).[1] There were no statistically significant differences in mortality between other PAH drugs and placebo and most studies were not sufficiently powered to detect a difference.[1] Macitentan demonstrated a statistically significant reduction in hospitalizations compared with placebo (RR 0.59; 95% CI, 0.43 to 0.81).[1] Other treatments, including ambrisentan 5 mg, bosentan, riociguat (both doses), sildenafil and tadalafil numerically favored reduction in hospitalizations compared to placebo but did not reach statistical significance.[1] When HRQoL was assessed, all drugs except bosentan showed improvement compared to placebo.[1] However, several different instruments were used to assess HRQoL, including Short-Form 36-Item health survey (SF-36), EuroQol 5-Dimensions questionnaire (EQ-5D), Living with Pulmonary Hypertension questionnaire, Minnesota Living with Heart Failure questionnaire, Chronic Heart Failure questionnaire, Nottingham Health Profile, and Dyspnea-Fatigue Rating.[1]

Safety

Safety data from total populations (treatment-naïve and treatment-experienced) were also evaluated in the systematic review. Respective to placebo, serious adverse events (SAEs) were less frequent with macitentan (45% vs. 55%), riociguat (11% vs. 18%), ambrisentan (9% vs. 16%), and tadalafil (9% vs. 55%). Treprostinil had frequent SAEs related to injection-site reactions (62% vs. 20% with placebo) which also led to higher discontinuations rates (7.7% vs. 0.4%). Bosentan, sildenafil, and epoprostenol did not demonstrate a difference in number of SAEs compared with placebo. Notable treatment-related AEs with a higher incidence than placebo were liver toxicity (bosentan); peripheral edema (riociguat, ambrisentan, bosentan and treprostinil); anemia (macitentan, riociguat and ambristentan); and hypotension (riociguat, epoprostenol and treprostinil). Epoprostenol and treprostinil were frequently associated with nausea, diarrhea, jaw pain, headache and injection-site reactions.

Zhang, et al. American Heart Journal (2015)[3]

Zhang, et al.[3] systematically studied the efficacy of oral PAH drugs on clinical worsening and mortality in patients with PAH. Randomized, double-blind, placebo-controlled, parallel-group trials that reported combined clinical worsening (CCW) events or all-cause mortality were eligible for inclusion in the review.[3] CCW events included all-cause mortality, lung or heart transplantation, hospitalization due to decompensated PAH and escalation of treatment (i.e., initiation of new therapy). Patients in the studies had to be diagnosed with PAH and treated with an oral dosage formulation of a PAH drug.[3] Studies that evaluated combination therapy with inhaled, subcutaneous or intravenous prostanoids were excluded.[3] Twenty-one RCTs (n=5,105) with a mean follow-up time of about 5 months were identified that met inclusion criteria, but 4 trials were subsequently excluded from analysis because a few patients had received concurrent inhaled, subcutaneous or intravenous PAH treatment.[3] Odds ratios (ORs) with 95% CIs were calculated for all-cause mortality and CCW events.[3] The mean difference or standard mean differences for continuous outcomes including 6MWD, PVR, mean PAP, mean right atrial pressure (RAP), and cardiac index were also calculated.[3] All analyses were based on the intention-to-treat principle using a fixed-effects or random-effects models depending on study heterogeneity.[3] Statistical

heterogeneity was assessed using the $_{x}^{2}$ test (significant if p<0.1) and I^2 test (significant if >50%).[3] Meta-analysis was performed for 3 drug classes: prostanoids, ERAs and PDE5 inhibitors.

More than half (63.6%) patients had IPAH or FPAH, and 20.2% had PAH associated with connective tissue disease.[3] Most of the patients were female with WHO FC II or III.[3] All studies but 1 reported baseline 6MWD and treatment effect on 6MWD, whereas only 8 studies reported baseline hemodynamic values and change from baseline.[3] The CCW event rate was significantly lower in the oral treatment group versus the placebo group (11.3% vs. 17.9%, respectively; OR 0.55; 95% CI, 0.47 to 0.64; p<0.001, heterogeneity p=0.166) but mortality rates did not significantly differ (2.5% vs. 3.3% for the treatment and placebo groups, respectively, OR 0.82; 95% CI, 0.61 to 1.10; p=0.192, heterogeneity p=0.986).[3] These results were not statistically dependent on trial characteristics.[3] Oral PAH drugs were associated with reduced risk for hospitalization (OR 0.52; 95% CI, 0.41 to 0.66) and reduced need to escalate therapy (OR 0.48; 95% CI, 0.26 to 0.90).[3] A pooled analysis was also performed by drug classes. Oral ERAs and PDE5 inhibitors reduced the OR of CCW by 50% and 53%, respectively (p<0.001), whereas oral prostanoids reduced the OR of CCW by 38% (p=0.014); oral riociguat also achieved a statistically significant reduction in the OR of 0.277 (p=0.015).[3] However, none of the oral drug classes achieved a statistically significant reduction in mortality versus placebo.[3] Change in 6MWD was significantly correlated with CCW in meta-regression analysis (p=0.006) and remained significant after adjustment for age, gender, drug class, WHO FC, and baseline 6MWD; however, there was no correlation between change in 6MWD and mortality (p=0.065).[3] Lastly, oral PAH treatment was also associated with significant improvement in PVR, mean PAP and mean RAP with both fixed- and random-effects models (p<0.001 for all).[3] However, there was again no association found between treatment effect on these hemodynamic parameters and all-cause mortality or CCW.[3]

Zheng, et al. Pulmonary Pharmacology & Therapeutics (2014)[2]

Zheng, et al.[2] also systematically assessed the efficacy of oral PAH drugs on mortality in patients with PAH. Similar methods to the Zhang, et al.[3] review were used to identify and assess RCTs of oral PAH drugs; however, since the authors were interested only in mortality outcomes, trials with endpoints limited to acute hemodynamic parameters were excluded.[2] In addition, studies that assessed sitaxsentan, which was withdrawn from the market due to liver toxicity, were also excluded.[2] Relative risks (RR) were calculated for dichotomous data and weighted mean differences (WMD), with 95% CI for continuous data.[2] The Cochran Q test and I^2 test were used to assess the magnitude of effect size heterogeneity.[2] When the effect size was homogenous, the data were analyzed with a fixed effect model; otherwise, a random-effects model was used.[2] Publication bias was assessed with funnel plots by Eggers' regression test.[2] Eighteen randomized, placebo-controlled trials (n=4,363) met inclusion criteria: 8 trials assessed ERAs, 4 trials assessed PD5 inhibitors, 5 trials assessed prostanoids, and 1 trial assessed the sGC stimulator riociguat.[2] In 17 trials, the predominant etiology was IPAH or familial PAH and most patients were in WHO FC III.[2] Median length of follow-up in the trials was 16 weeks (range 12 to 96 weeks), with only 1 long-term, event-driven trial, which studied macitentan using a composite primary endpoint of morbidity and mortality.[2] The primary endpoint was 6MWD (alone or in combination with another outcome) in 14 trials; other primary outcomes in the trials included PVR, clinical worsening or maximal oxygen consumption.[2] Mortality was reported in 18 trials (n=4,363) but no individual trial showed a statistically significant reduction in all-cause mortality.[2]

As a drug class, ERAs (RR 0.82; 95% CI, 0.52 to 1.30; p=0.396) and prostanoids (RR 0.90; 95% CI, 0.46 to 1.79; p=0.773), and the sGC simulator riociguat (RR 0.40; 95% CI, 0.08 to 1.94; p=0.254), were not associated with a statistically significant reduction in all-cause mortality; however, PDE5 inhibitors as a class were associated with a significant mortality reduction compared to placebo (RR 0.22; 95% CI, 0.07 to 0.71; p=0.011).[2] Secondary outcomes evaluated included clinical worsening, which showed a significant improvement with all drug classes but the oral prostanoids.[2] WHO FC improved by at least 1 grade in 20.7% of the patients studied in these trials.[2] By drug class, ERAs and PDE5 inhibitors significantly improved WHO FC, whereas oral prostanoids did not.[2] The meta-analysis also found statistically significant improvement in 6MWD with each of the 3 drug classes: oral PDE5 inhibitors improved 6MWD by 39 meters, oral ERA agents improved 6MWD by 35 meters, and oral prostanoids improved 6MWD by 20 meters.[2] Lastly, oral prostanoids were associated with increased withdrawal due to

adverse effects (RR 3.41; 95% CI, 2.06 to 5.63; p=0.000), whereas oral ERAs (RR 0.92; 95% CI, 0.66 to 1.28; p=0.626) and PDE5 inhibitors (RR 0.64; 95% CI, 0.39 to 1.04; p=0.072) did not increase incidence of withdrawal from adverse effects.[2] For the outcomes assessed, no significant heterogeneity between the trials for each drug class was found.[2]

Although there was an overlap for the majority of trials included in both systematic reviews by Zhang, et al.[3] and Zheng et al.[2], it should be noted that there were some differences in some of the included trials that account for the small differences in their results. First, one study included in the Zheng, et al.[2] review but excluded by Zhang, et al.,[3] largely influenced the overall mortality benefit with the PDE5 inhibitors calculated by Zheng, et al.[2] Zhang, et al. also included trials that evaluated sitaxentan, an oral ERA that was removed from the market due to risk for liver toxicity. Limitations between these systematic reviews are largely the same: the majority of trials included had a small sample sizes and short duration of follow-up, which made it difficult to assess mortality and other meaningful long-term clinical outcomes. Clinical worsening outcomes were also defined somewhat differently between individual trials and some of the trials did not adequately report some secondary outcomes, which may have led to reporting bias. In addition, publication bias favoring the publication of positive studies could not be excluded, though the funnel-plot analyses of identified trials did not identify asymmetry.

Rival, et al. CHEST (2014)[13]

Rival, et al.[13] systematically assessed the efficacy of PAH-specific therapies to improve HRQoL. Patient-perceived wellbeing is assessed through a questionnaire that includes physical, social and psychological domains in relation to how they are affected by health. A systematic review of these results was conducted in order to strengthen confidence in how PAH therapies might affect HRQoL.[13] Randomized, placebo-controlled trials longer than 6 weeks' duration that evaluated the effect of PAH therapies using HRQoL questionnaires in adults were included.[13] Seventeen articles reporting on 14 trials were identified that met inclusion criteria.[13] The median study duration was 12 weeks (range 6 to 104 weeks).[13] Most patients had IPAH or PAH associated with connective tissue disease.[13] A variety of HRQoL questionnaires were used, but the generic Medical Outcomes Study 36-item Short Form (SF-36) questionnaire was most commonly used.[13] In addition, for most of the questionnaires used, the MCID in scores in the setting of PAH is unknown.[13] Most RCTs that evaluated HRQoL included it as a secondary or exploratory endpoint that was only minimally detailed in the trials, often with only p-values provided.[13] Therefore, a meta-analysis of the data was not performed, though many trials demonstrated significant improvement in HRQoL scores (especially for physical domains).[13]

New Guidelines:

Canadian Drug Expert Committee (2015)[7]

Recommendations published by the Canadian Drug Expert Committee (CDEC) were informed by the CADTH systematic review.[1] The CDEC acknowledged that medical specialists who work with PAH are best suited to prescribe these medications given the nature of the disease as well as the complexity and costs of drug regimens.[7]

An oral PDE5 inhibitor (sildenafil or tadalafil) is the preferred initial therapy for adult patients with PAH in WHO FC II and III.[7] CADTH meta-analyses demonstrated that monotherapy of available oral PAH drugs are similarly efficacious in slowing WHO FC and clinical worsening, and PDE5 inhibitors were the most cost-effective options.[7] However, there is no evidence to guide the duration of treatment with sildenafil or tadalafil before changing to or adding another drug.[7] Thus, the decision to change therapy or combine therapy with the PDE5 inhibitor should be made by a PAH specialist based on patient-specific factors and response (effectiveness and harms).[7] For patients unable to receive sildenafil or tadalafil, there is insufficient evidence to make a recommendation with respect to specific alternative initial therapies.[7]

There is insufficient evidence to make a recommendation for initial therapy in PAH patients with WHO FC I and WHO FC IV at this time.[7] Patients with WHO FC I have not been represented in RCTs (<1%).[7] For patients in WHO FC III or IV, IV epoprostenol is the only drug that has shown reduced mortality compared with placebo; however, patients with more severe disease made up a large portion of the subjects in the epoprostenol studies (74% FC III and 26% FC IV).[7]

There are several limitations to the evidence that prohibited the CDEC from making more specific recommendations. First, the key outcome studied in most RCTs was change in 6MWD from baseline, a measure that does not reliably reflect clinically relevant outcomes such as mortality, hospitalizations, or initiation of rescue therapy.[7] Second, some patients may not achieve satisfactory disease control on a single drug and may require additional medications due to the progressive nature of the disease, and combination therapy should be used in such patients.[7] Four RCTs demonstrated that sequential combination therapy can improve outcomes versus monotherapy.[7] There is insufficient evidence that assesses triple combination therapy.[7] Lastly, no specific recommendations could be made to subgroups of patients (based on disease severity or other disease characteristics) who may benefit more from specific drugs or combinations of drugs based on insufficient evidence.[7]

<u>European Society of Cardiology and European Respiratory Society (2015)</u>[11]

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) recently updated their clinical practice guideline on the management of PH. A comprehensive search for published evidence was performed.[11] Identified evidence was critically appraised with the level of evidence graded (defined in Table 3) and strength of recommendation given (defined in Table 4) for each management option.[11]

Table 3. ESC/ERS Strength of Recommendations.[11]

Class I	Given treatment is beneficial, useful and effective	Recommendation indicated
Class II	Divergence of opinion whether treatment is useful/efficacious	
Class IIa	Weight is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy not well established	May be considered
Class III	Given treatment is not useful or effective, and may even be harmful	Not recommended

Table 4. ESC/ERS Level of Evidence Grades.[11]

Level of Evidence A	Data derived from multiple RCTs or meta-analyses
Level of Evidence B	Data derived from single RCT or large non-randomized studies
Level of Evidence C	Consensus opinion, retrospective studies or registries

Recommendations and evidence grades specific to management of PAH are summarized in Table 5.

Table 5. Recommendations for Drug Monotherapy Options in PAH According to WHO FC.[11]

WHO FC II	WHO FC III	WHO FC IV
ERAs: • Ambrisentan, oral (Class **I**, Level **A**) • Bosentan, oral (Class **I**, Level **A**) • Macitentan, oral (Class I, Level B) **PDE5 Inhibitors:** • Sildenafil, oral (Class **I**, Level **A**) • Tadalafil, oral (Class I, Level B) **Prostanoids:** • - **IP Receptor Agonists:** • Selexipag, oral (Class I, Level B) **sGC Stimulators:** • Riociguat, oral (Class I, Level B)	**ERAs:** • Ambrisentan, oral (Class **I**, Level **A**) • Bosentan, oral (Class **I**, Level **A**) • Macitentan, oral (Class I, Level B) **PDE5 Inhibitors:** • Sildenafil, oral (Class **I**, Level **A**) • Tadalafil, oral (Class I, Level B) **Prostanoids:** • Epoprostenol, IV (Class **I**, Level **A**) • Iloprost, inhaled (Class I, Level B) • Treprostinil, SC (Class I, Level B) • Treprostinil, inhaled (Class I, Level B) • Treprostinil, IV (Class IIa, Level C) • Treprostinil, oral (Class IIb, Level B) **IP Receptor Agonists:** • Selexipag, oral (Class I, Level B) **sGC Stimulators:** • Riociguat, oral (Class I, Level B)	**ERAs:** • Ambrisentan, oral (Class IIb, Level C) • Bosentan, oral (Class IIb, Level C) • Macitentan, oral (Class IIb, Level C) **PDE5 Inhibitors:** • Sildenafil, oral (Class IIb, Level C) • Tadalafil, oral (Class IIb, Level C) **Prostanoids:** • Epoprostenol, IV (Class **I**, Level **A**) • Iloprost, inhaled (Class IIb, Level C) • Treprostinil, SC (Class IIb, Level C) • Treprostinil, inhaled (Class IIb, Level C) • Treprostinil, IV (Class IIb, Level C) **IP Receptor Agonists:** • - **sGC Stimulators:** • Riociguat, oral (Class IIb, Level C)

Combination therapy using 2 or more classes of drugs simultaneously may be applied sequentially or initially. The rationale for initial combination therapy is based on the known mortality of PAH.[11] However, sequential combination therapy has been more widely studied and is most widely utilized in clinical trials and in clinical practice, though a statistically significant mortality reduction with combination therapy has not yet been achieved.[11] Recommendations and evidence for the use of specific drug combination options are presented in Table 6 for initial combination therapy and in Table 7 for sequential combination therapy.

Table 6. Recommendations for Initial Drug Combination Therapy for PAH According to WHO FC.[11]

WHO FC II	WHO FC III	WHO FC IV
• Ambrisentan + tadalafil, oral (Class I, Level B) • Other oral ERA + oral PDE5 inhibitor (Class IIa, Level C)	• Ambrisentan + tadalafil, oral (Class I, Level B) • Other oral ERA + oral PDE5 inhibitor (Class IIa, Level C) • Oral bosentan + oral sildenafil + IV epoprostenol (Class IIa, Level C) • Oral bosentan + IV epoprostenol (Class IIa, Level C) • Other oral ERA or PDE5 inhibitor + SC treprostinil (Class IIb, Level C) • Other oral ERA or PDE5 inhibitor + other IV prostanoid (Class IIb, Level C)	• Oral bosentan + oral sildenafil + IV epoprostenol (Class IIa, Level C) • Oral bosentan + IV epoprostenol (Class IIa, Level C) • Ambrisentan + tadalafil, oral (Class IIb, Level C) • Other oral ERA + oral PDE5 inhibitor (Class IIb, Level C) • Other oral ERA or PDE5 inhibitor + SC treprostinil (Class IIb, Level C) • Other oral ERA or PDE5 inhibitor + other IV prostanoid (Class IIb, Level C)

Table 7. Recommendations for Sequential Drug Combination Therapy for PAH According to WHO FC.[11]

Sequential Combination Regimen	WHO FC II	WHO FC III	WHO FC IV
Macitentan added to sildenafil Riociguat added to bosentan	Class I, Level B Class I, Level B	Class I, Level B Class I, Level B	Class IIa, Level C Class IIa, Level C
Selexipag added to an ERA and/or PDE5 inhibitor	Class I, Level B	Class I, Level B	Class IIa, Level C
Sildenafil added to epoprostenol	Insufficient	Class I, Level B	Class IIa, Level B
Treprostinil inhaled added to sildenafil or bosentan	Class IIa, Level B	Class IIa, Level B	Class IIa, Level C
Iloprost inhaled added to bosentan	Class IIb, Level C	Class IIb, Level B	Class IIb, Level C
Tadalafil added to bosentan	Class IIa, Level C	Class IIa, Level C	Class IIa, Level C
Ambrisentan added to sildenafil	Class IIb, Level C	Class IIb, Level C	Class IIb, Level C
Bosentan added to epoprosentol	Insufficient	Class IIb, Level C	Class IIb, Level C
Bosentan added to sildenafil	Class IIb, Level C	Class IIb, Level C	Class IIb, Level C
Other double combinations	Class IIb, Level C	Class IIb, Level C	Class IIb, Level C
Other triple combinations	Class IIb, Level C	Class IIb, Level C	Class IIb, Level C
Riociguat added to sildenafil or other PDE5 inhibitor	Class III, Level B	Class III, Level B	Class III, Level B

American College of Chest Physicians (2014)[9]

The updated CHEST guideline addresses only drugs approved by the FDA for the management of PAH, with the exception of a CCB, which are also included because of their use in a small but important subgroup of vasoreactive patients with PAH. The rating of the quality of the entire body of evidence for each intervention and outcome for PAH was assessed. Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was used to summarize and grade pooled evidence.[9] Evidence ratings started as high quality and were downgraded based on domains of risk of bias, precision, consistency, directness and publication bias.[9] The letter grade (A, B, C or Insufficient) was assigned based on the evidence level of the body of literature supporting each intervention and outcome comparison.[9] To be considered C-level evidence, 2 or more studies that addressed the specific intervention and outcome were required.[9] An evidence-based guideline was pursued when the evidence level was determined to be "A" (high-quality evidence), "B" (moderate-quality evidence), or "C" (low-quality evidence). A consensus-based statement was issued where the evidence was deemed insufficient.[9] A number grade (1 or 2) was also assigned reflect the recommendation as strong (1) or weak (2) on the basis of perceived benefits and harms of the treatment.[9]

Recommendations are organized by WHO FC as it is frequently a starting point in treatment decisions and a basis upon which drugs are approved by the FDA.[9] In general, management of patients with PAH should be collaborative and closely coordinated between local physicians and providers with expertise in PAH, which may involve cardiologists, pulmonologists, rheumatologists, and primary care (*consensus*).[9]

The following drug therapy recommendations are highlighted from the CHEST guideline:

Treatment-naïve Patients in WHO FC I:

- This population of patients should be continuously monitored for development of symptoms that would signal disease progression and warrant initiation of pharmacotherapy (*consensus*).[9] Any causes that may contribute to PAH, such as sleep apnea and hypertension, should be aggressively treated (*consensus*). In patients that demonstrate acute vasoreactivity upon testing, a trial of a CCB (i.e., amlodipine, diltiazem, nifedipine) should be initiated unless there are contraindications or right-sided heart failure is present (*consensus*).[9]

Treatment-naïve Patients in WHO FC II:

- Patients who are not candidates for a CCB should be initiated on monotherapy.[9] Options for initial monotherapy include an ERA, PDE5 inhibitor, or riociguat:
    - The ERA ambrisentan may be used to improve 6MWD (*Grade 1C*); bosentan or macitentan are other ERAs that can be used to delay time to clinical worsening (*consensus*);
    - PDE5 inhibitors sildenafil (*Grade 1C*) or tadalafil (*consensus*) may be used to improve 6MWD; or
    - Riociguat can be used to improve 6MWD (*consensus*) and WHO FC (*consensus*), and delay time to clinical worsening (*consensus*).
    - Parenteral or inhaled prostanoids should *not* be chosen as initial therapy or as second-line agents who have not met treatment goals (*consensus*).[9]

Treatment-naïve Patients in WHO FC III:

- Patients who are not candidates for a CCB should be initiated on monotherapy.[9] Again, options for initial monotherapy include an ERA, PDE5 inhibitor, or riociguat:
    - The ERA bosentan may be used to improve 6MWD (*Grade 1B*) and to decrease hospitalizations related to PAH in the short-term (*Grade 2C*); ambrisentan may also be used to improve 6MWD (*Grade 1C*); alternatively, macitentan can be used to improve WHO FC (*consensus*) and delay the time to clinical worsening (*consensus*);
    - PDE5 inhibitors sildenafil (*Grade 1C*) or tadalafil (*consensus*) may be used to improve 6MWD or to improve WHO FC (*consensus*); or

- Riociguat can be used to improve 6MWD (*consensus*) or WHO FC (*consensus*).
- Patients who have evidence of rapid disease progression or poor clinical prognosis should be initiated on a parenteral prostanoid, such as continuous IV epoprostenol to improve WHO FC (*consensus*), or continuous IV epoprostenol, treprostinil, or continuous SC treprostinil to improve 6MWD (*consensus*).[9]

Treatment-experienced Patients in WHO FC III:

- Patients with evidence of disease progression or poor clinical prognosis despite treatment with oral agents should be initiated on a parenteral or inhaled prostanoid[9]:
  - Inhaled may be used treprostinil to improve 6MWD (*Grade 2C*) in patients who remain symptomatic on stable and appropriate doses of an ETRA or PDE5 inhibitor; alternatively, inhaled iloprost can be used to improve WHO FC (*consensus*) and delay time to clinical worsening (*consensus*); or
  - Continuous IV epoprostenol can be used to improve WHO FC (*consensus*) or 6MWD (*consensus*); continuous IV treprostinil can also be used to improve 6MWD (*consensus*).[9]

Patients in WHO FC IV:

- Patients should be initiated on a parenteral prostanoid, such as[9]:
  - Continuous IV epoprostenol can be used to improve WHO FC (*consensus*) and 6MWD (*consensus*); alternatively, continuous IV treprostinil or continuous SC treprostinil can be used to improve 6MWD (*consensus*).[9]
  - Treatment-naïve patients unable to manage parenteral prostanoid therapy may be initiated on an inhaled prostanoid in combination with an ERA, such as bosentan to improve 6MWD (*Grade 2B*) and inhaled iloprost to improve 6MWD (*consensus*) and WHO FC (*consensus*); inhaled treprostinil (in combination only) can also be used to improve 6MWD (*consensus*).[9]

New Safety Alerts:
None identified.

New Formulations or Indications:
None identified.

Randomized Controlled Trials:
A total of 47 citations were manually reviewed from the literature search. After further review, all but 2 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). These trials are briefly described in the Table 8 below. Full abstracts are included in **Appendix 2**.

Table 8. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Endpoint	Results
Galie, et al.[5] MC, DB, RCT	1. ambrisentan 10 mg + tadalafil 40 mg (n=302) 2. ambrisentan 10 mg + placebo (n=152) 3. tadalafil 40 mg + placebo (n=151)	▪Mean age 54 years ▪78% female ▪WHO FC II/III PAH (69% FC III) ▪Treatment-naïve ▪PAP ≥25 mmHg	Composite Clinical Worsening: time-to-event of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response.	1. ambrisentan + tadalafil (18%) 2. ambrisentan + placebo (34%) 3. tadalafil 40 mg + placebo (28%) 1. vs. 2. [HR 0.48; 95% CI 0.31-0.72, p<0.001] 1. vs. 3. [HR 0.53; 95% CI 0.34-0.83, p=0.005] Note: Composite endpoint primarily driven by reduction in hospitalizations for PAH. Mean duration of treatment was 609 days (no statistically significant difference between groups).
McLaughlin, et al.[4] MC, DB, RCT	1. bosentan 62.5-125 mg BID (n=159) 2. placebo (n=175) All patients had been on, and remained on, sildenafil ≥20 mg TID	▪Mean age 54 years ▪76% female ▪WHO FC II/III PAH ▪6MWD 150-480 m ▪Sildenafil ≥20 mg TID for ≥3 months before study (no other PAH drugs)	Composite Clinical Worsening: time-to-event of death, hospitalization for worsening PAH or initiation of IV prostanoid therapy, atrial septostomy, lung transplant, or worsening PAH.	1. bosentan (42.8%) [HR 0.83; 97.31% CI 0.58-1.19, p=0.2508] 2. placebo (42.8%) Note: mean duration of treatment was 40 months for the placebo group and 38 months for the bosentan group. Median daily sildenafil dose was 60.0 mg for both groups.

Abbreviations: 6MWD = 6-minute walk distance; BID = twice daily; CI = confidence interval; DB = double-blind; IV = intravenous; MC = multi-centered; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; RCT = randomized, controlled trial; SC = subcutaneous; TID = three-times daily; WHO FC = World Health Organization Functional Class.

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Pharmacology and Pharmacokinetic Properties:

The mechanism of action and specific pharmacokinetic properties of selexipag are listed in Table 9.

Table 9. Pharmacology and Pharmacokinetic Properties.[12]

Mechanism of Action	Selexipag and its active metabolite are selective IP prostacyclin receptor agonists
Absorption	Time to maximum concentration is 1-3 hours (selexipag) and 3-4 hour (active metabolite)
Distribution and Protein Binding	Both selexipag and its active metabolite are highly bound (99%) to plasma proteins (i.e., albumin, alpha 1-acid glycoprotein)
Elimination	Primarily eliminated through metabolism
Half-Life	0.8-2.5 hours (active metabolite 6.2-13.5 hours)
Metabolism	Hydrolyzed by carboxylesterase 1 to active metabolite (37-fold more potent than selexipag), followed by oxidative metabolism through CYP3A4 and CYP2C8 and glucuronidation of the metabolite by UGT1A3 and UGT2B7

Clinical Efficacy:

FDA approval of selexipag is based on a single trial that assessed the efficacy of selexipag versus placebo in PAH WHO FC II or III patients with or without background ERA and PDE5 inhibitor therapy.[14] The trial was a multicenter, double-blind, randomized, parallel-group, placebo-controlled, event-driven, phase 3 study.[6] Patients were randomized 1:1 to placebo or selexipag 200 mcg twice daily (BID). Concomitant use of prostanoids was prohibited. The selexipag dose was increased weekly during a 12-week dose titration phase by 200 mcg per dose until the maximum tolerable dose was reached. The maximum allowed dose was 1600 mcg BID. After 12 weeks, patients entered the maintenance phase of the study.

The end of the treatment period was defined for each patient as 7 days after the last dose of selexipag or placebo. The end of the treatment period occurred at the end of the study (for patients who did not have a primary endpoint event), after first occurrence of a primary endpoint, or after premature discontinuation of the drug (e.g., due to an adverse event, etc.). The end of the study was declared when the pre-specified number of primary endpoint events in the study population was reached. The primary endpoint was time to first event of (a) all-cause mortality, (b) hospitalization for worsening PAH, (c) initiation of parental prostanoid or chronic oxygen, (d) confirmed 15% decrease in 6MWD plus worsened WHO FC or need for additional PAH therapy. Secondary endpoints included components of the primary composite endpoint.

Details of the study are available in Table 10. The study population was 80% female, 13% from the U.S., and had a median age of 49 years. Nearly all patients at baseline were either in WHO FC II (45.8%) or WHO FC III (52.5%). Over 26 weeks, 26% of patients receiving selexipag discontinued treatment, mostly for adverse events, versus 17% in the placebo group. Overall, 397 patients experienced the primary endpoint (41.6% in the placebo group and 27.0% in the selexipag group; HR 0.60; 99% CI, 0.46 to 0.78; $p<0.001$). The primary drivers behind the composite endpoint were a lower incidence of disease progression with selexipag (6.6% vs. 17.2% with placebo) and hospitalization for worsening PAH with selexipag (13.6% vs. 18.7% with placebo). Death from any cause occurred more frequently in patients in the selexipag group (4.9%) versus the placebo group (3.1%); however, all-cause mortality (17.4% vs. 18.0%, respectively) and mortality due to PAH

(12.2% vs. 14.3%, respectively) was equal between the two groups when events up to the end of the study were assessed and analyses included patients who chose to remain enrolled after a non-fatal primary endpoint was reached. The FDA's initial concerns were alleviated by these subsequent data.[14]

Subgroup analyses of the primary endpoint were performed on pre-specified dose strata: low doses (200 or 400 mcg BID), medium doses (600, 800, or 1000 mcg BID), and high doses (1200, 1400 or 1600 mcg BID). A total of 23.2% of patients received a maintenance dose of selexipag in the low-dose stratum, 31.2% received a maintenance dose in the medium-dose stratum, and 42.9% received a maintenance dose in the high-dose stratum. The treatment effect of selexipag with respect to the primary endpoint was consistent across the dosing strata. In another pre-specified subgroup analysis, the treatment effect was similar in patients who were already receiving both ERA and PDE5 inhibitor therapy (33%), one of the treatments (15% on an ERA; 32% on a PDE5 inhibitor), or none.

At week 26, the 6MWD had decreased by a median of 9.0 m from baseline in the placebo group and had increased by 4.0 m from baseline in the selexipag group (difference 12.0 m; 99% CI, 1.0 to 24.0 m; p=0.003). The difference seen between the groups in 6MWD is miniscule compared with other therapies but was somewhat attributable to imputation rules.[14] There was not a statistically significant difference between the groups with respect to the number of patients who did not experience worsening WHO FC (74.9% in the placebo group vs. 77.8% in the selexipag group; OR 1.16; 99% CI, 0.81 to 1.66; p=0.28). In addition, there were no statistically significant differences in mortality due to PAH (14.3% in the placebo group vs. 12.2% in the selexipag group; HR 0.86 [95% CI, 0.63 to 1.18; p=0.18]) or all-cause mortality (18.0% in the placebo group vs. 17.4% in the selexipag group; HR 0.97 [95% CI, 0.74 to 1.28; p=0.42]) at the end of the study period.

Overall, there was low concern for risks of bias, though the attrition rates were high but not unexpected for this population. The applicability of the study's results to the OHP PAH population is of moderate concern as few centers were located in the U.S. and the majority of patients were of Asian and Eastern European populations.

Clinical Safety:
Overall, 7.1% of patients in the placebo group and 14.3% of patients in the selexipag group prematurely discontinued their medication due to an adverse event. The most frequent adverse events leading to early discontinuation of selexipag were headache, nausea and diarrhea. The most common adverse effects were similar to those observed in patients who receive prostanoid therapy. The frequencies of these adverse effects, including numbers needed to harm, are detailed in Table 5. No serious adverse events were reported more frequently in the selexipag group compared to the placebo group. However, hyperthyroidism occurred in 8 patients in the selexipag group (and led to early discontinuation in 1 patient) but none in the placebo group (p<0.004). Anemia also occurred more frequently in the selxipag group than in the placebo group (8.3% vs. 5.4%, respectively; p=0.05) with a hemoglobin level less than 8 g/dL occurring in 1.3% of patients in the selexipag group and 0.7% of patients in the placebo group (p=0.38). According to FDA analysis, the safety profile of selexipag is similar to that of other systemic vasodilators.[14]

Comparative Clinical Efficacy:
Clinically Relevant Endpoints:
1) Mortality
2) Hospitalizations
3) Heart or lung transplant
4) Atrial septostomy
5) Change in WHO FC

Primary Study Endpoint:
1) Composite endpoint of death or complication from PAH

Table 10. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Sitbon, et al.[6] MC, DB, PG, PC RCT Phase 3 Sponsor: Actelion, Ltd	1. Selexipag 200 mcg BID and titrated by 200 mcg to maximum tolerated dose (NTE 1600 mcg BID) [S] 2. Placebo [P] 1:1 randomization 12-week dose adjustment phase, followed by maintenance phase Median duration for selexipag: 70.7 wks Median duration for placebo: 63.7 wks	Demographics: Females: 79.8% Mean age: 48.1 y IPAH: 56.1%% WHO FC II: 45.8% WHO FC III: 52.5% 6MWD: 353.2 m Treatment-naïve: 20.4% Key Inclusion Criteria: ▪Age 18-75 years ▪IPAH; FPAH; or PAH associated with HIV, drug use/toxin exposure, connective tissue disease or repaired congenital systemic-to-pulmonary shunts ▪PVR ≥5 Wood units (400 dyn•sec•cm^{-5}) ▪6MWD 50-450 m Key Exclusion Criteria: ▪prostanoid therapy	ITT: 1. 574 2. 582 PP: 1. 574 2. 582 Attrition: 1. 22.6% 2. 15.1%	Primary Endpoint: Death or complication related to PAH* Selexipag: 27.0% Placebo: 41.6% HR 0.60 (99% CI, 0.46 to 0.78; p<0.001) Secondary Endpoints (in order of hierarchy): Change in 6MWD from baseline to week 26: S: +4.0 m vs. P: -9.0 m MD 12.0 m (99% CI, 1.0 to 24.0 m; p=0.003) Absence of WHO FC worsening to week 26: S: 77.8% vs. P: 74.9% OR 1.16 (99% CI, 0.81 to 1.66; p=0.28) Death due to PAH: S: 12.2% vs. P: 14.3% HR 0.86 (95% CI, 0.63 to 1.18; p=0.18) All-cause mortality: S: 17.4% vs. P: 18.0% HR 0.97 (95% CI, 0.74 to 1.28; p=0.42)	14.6%/7 NA NS NS NS	Early D/C due to AE: S: 14.3% P: 7.1% P<0.001 ≥1 SAE: S: 43.8% P: 47.1% p=0.26 Headache: S: 65.2% P: 32.8% p<0.001 Diarrhea: S: 42.4% P: 19.1% p<0.001 Nausea: S: 33.6% P: 18.5% p<0.001 Pain in Jaw: S: 25.7% P: 6.2% p<0.001	7.2%/13 NS 32.4%/3 23.3%/4 15.1%/6 19.5%/5	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized centrally via IWRS/IVRS. Performance Bias: (low) double-blinded by matching placebo tablets. Detection Bias: (low) collection, management and analysis of data performed by sponsor; however, data assessment was blinded. Statistical assumptions used to power study not referenced. True ITT analysis of results performed. Attrition Bias: (high) significantly more patients discontinued study treatment due to adverse events which may have unblinded patients and study personnel. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: 20.4% treatment-naïve or concomitantly taking PDE5-inhibitor (32.4%) or ERA (14.7%), or both (32.5%), at stable doses. Only 16.7% were North American. Intervention: Comparator: Outcomes: primary composite outcome a time-to-event analysis driven by reduction in disease progression (6.6% vs. 17.2%) Setting: 181 outpatient clinic sites in 39 countries, primarily in Asian and Eastern European settings.

Abbreviations [alphabetical order]: 6MWD = 6-minute walk distance; AE = adverse event; ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; DB = double blind; ERA = endothelin-receptor antagonist; FPAH = familial (heritable) pulmonary arterial hypertension; HIV = human immunodeficiency virus infection; HR = hazard ratio; IPAH = idiopathic pulmonary arterial hypertension; ITT = intention to treat; IWRS/IVRS = interactive web/voice response system; m = meters; mcg = micrograms; MC = multi-centered; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; O_2 = oxygen; PAH = pulmonary arterial hypertension; PC = placebo-controlled; PDE5 = phosphodiesterase-5; PG = parallel group; PP = per protocol; PVR = pulmonary vascular resistance; RCT = Randomized Controlled Trial; SAE = serious adverse event; WHO FC = World Health Organization Functional Class.
*Complication of PAH defined as: disease progression (15% reduction in 6MWD plus worsening WHO FC or need for additional PAH treatment); worsening of PAH that led to hospitalization, initiation of parenteral prostanoid or long-term O_2; or need for lung transplant or balloon atrial septostomy.

References:

1. Tran K, Coyle K, 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.

2. Zheng Y, Ma H, Hu E, Liu G, Chen G, Xiong C. Oral targeted therapies in the treatment of pulmonary arterial hypertension: a meta-analysis of clinical trials. *Pulmonary Pharmacology & Therapeutics*. 2014;29:241-249. doi:10.1016/j.pupt.2014.08.005.

3. Zhang H, Zhang R, Jiang X, Sun K, Wu D, Jing Z. Effects of oral treatments on clinical outcomes in pulmonary arterial hypertension: A systematic review and meta-analysis. *Am Heart J*. 2015;170:96-103. doi:10.1016/j.ahj.2015.04.003.

4. McLaughlin V, Channick R, Ghofrani H, LeMair J, Naeije R, Packer M. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J*. 2015;46:405-413. doi:10.1183/13993003.02044-2014.

5. Galie N, Barbera J, Frost A, Ghofrani H, Hoeper M, McLaughlin V. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med*. 2015;373:834-844. doi:10.1056/NEJMoa1413687.

6. Sitbon O, Channick R, Chin K, Frey A, Gaine S, Galie N. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373:2522-2533. doi:10.1056/NEJMoa1503184.

7. Tran K, Coyle K, Jabr M, Coyle D, Boucher M, Mielniczuk L. Drugs for pulmonary arterial hypertension: comparative efficacy, safety, and cost-effectiveness - Recommendations Report. *Canadian Agency for Drugs and Technologies in Health*. March 2015.

8. Drug Class Update: Oral/Inhaled Pulmonary Arterial Hypertension Agents. Drug Use Research & Management Program, Oregon State University College of Pharmacy; July 2014. Available at http://www.orpdl.org/durm/meetings/meetingdocs/2014_07_31/archives/2014_07_31_PAHUpdateFinal_630ks.pdf. Accessed January 8, 2016.

9. Taichman D, Ornelas J, Chung L, Klingler J, Lewis S, Mandel J. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST Guideline and Expert Panel Report. *CHEST*. 2014;146:449-475. doi:10.1378/chest.14-0793.

10. Barst R, McGoon M, Torbicki A, Sitbon O, Krowka M, Olschewski H. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43:40S - 47S. doi:10.1016/j.jacc.2004.02.032.

11. Galie N, Humbert M, Vachiery J, Gibbs S, Lang I, Torbicki A. 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). *Eur Heart J*. 2015;First published online: 29 August 2015. doi:10.1093/eurheartj/ehv317.

12. Uptravi (selexipag) [Prescribing Information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc., December 2015.

13. Rival G, Lacasse Y, Martin S, Bonnet S, Provencher S. Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. *CHEST*. 2014;146:686-708. doi:10.1378/chest.13-2634.

14. FDA Summary Review of Selexipag. Center for Drug Evaluation and Research, application number: 207947Orig1s000. Avaliable at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207947Orig1s000SumR.pdf. Accessed February 8, 2016.

Author: Andrew Gibler, Pharm.D. Date: March 2016

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	REVATIO	SILDENAFIL CITRATE	Y
ORAL	TABLET	SILDENAFIL	SILDENAFIL CITRATE	Y
ORAL	TABLET	TRACLEER	BOSENTAN	Y
INHALATION	AMPUL-NEB	TYVASO	TREPROSTINIL	N
INHALATION	AMPUL-NEB	TYVASO	TREPROSTINIL/NEB ACCESSORIES	N
INHALATION	AMPUL-NEB	TYVASO	TREPROSTINIL/NEBULIZER/ACCESOR	N
INHALATION	AMPUL-NEB	VENTAVIS	ILOPROST TROMETHAMINE	N
INJECTION	VIAL	REMODULIN	TREPROSTINIL SODIUM	N
INTRAVEN	VIAL	EPOPROSTENOL SODIUM	EPOPROSTENOL SODIUM (GLYCINE)	N
INTRAVEN	VIAL	FLOLAN	EPOPROSTENOL SODIUM (GLYCINE)	N
INTRAVEN	VIAL	VELETRI	EPOPROSTENOL SODIUM (ARGININE)	N
ORAL	TABLET	ADCIRCA	TADALAFIL	N
ORAL	TABLET	ADEMPAS	RIOCIGUAT	N
ORAL	TABLET	LETAIRIS	AMBRISENTAN	N
ORAL	TABLET	OPSUMIT	MACITENTAN	N
ORAL	TABLET ER	ORENITRAM ER	TREPROSTINIL DIOLAMINE	N
INTRAVEN	VIAL	REVATIO	SILDENAFIL CITRATE	
INTRAVEN	VIAL	SILDENAFIL CITRATE	SILDENAFIL CITRATE	
ORAL	SUSP RECON	REVATIO	SILDENAFIL CITRATE	

Appendix 2: Abstracts of Clinical Trials

Galie N, Barbera JA, Frost AE, et a. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med*. 2015; 373:834-44. DOI: 10.1056/NEJMoa1413687

BACKGROUND Data on the effect of initial combination therapy with ambrisentan and tadalafil on long-term outcomes in patients with pulmonary arterial hypertension are scarce.

METHODS In this event-driven, double-blind study, we randomly assigned, in a 2:1:1 ratio, participants with World Health Organization functional class II or III symptoms of pulmonary arterial hypertension who had not previously received treatment to receive initial combination therapy with 10 mg of ambrisentan plus 40 mg of tadalafil (combination-therapy group), 10 mg of ambrisentan plus placebo (ambrisentan monotherapy group), or 40 mg of tadalafil plus placebo (tadalafil monotherapy group), all administered once daily. The primary end point in a time-to-event analysis was the first event of clinical failure, which was defined as the first occurrence of a composite of death, hospitalization for worsening pulmonary arterial hypertension, disease progression, or unsatisfactory long-term clinical response.

RESULTS The primary analysis included 500 participants; 253 were assigned to the combination-therapy group, 126 to the ambrisentan-monotherapy group, and 121 to the tadalafil-monotherapy group. A primary end-point event occurred in 18%, 34%, and 28% of the participants in these groups, respectively, and in 31% of the pooled monotherapy group (the two monotherapy groups combined). The hazard ratio for the primary end point in the combination-therapy group versus the pooled-monotherapy group was 0.50 (95% confidence interval [CI], 0.35 to 0.72; P<0.001). At week 24, the combination-therapy group had greater reductions from baseline in N-terminal pro–brain natriuretic peptide levels than did the pooled-monotherapy group (mean change, −67.2% vs. −50.4%; P<0.001), as well as a higher percentage of patients with a satisfactory clinical response (39% vs. 29%; odds ratio, 1.56 [95% CI, 1.05 to 2.32]; P = 0.03) and a greater improvement in the 6-minute walk distance (median change from baseline, 48.98 m vs. 23.80 m; p<0.001). The adverse events that occurred more frequently in the combination-therapy group than in either monotherapy group included peripheral edema, headache, nasal congestion, and anemia.

CONCLUSIONS Among participants with pulmonary arterial hypertension who had not received previous treatment, initial combination therapy with ambrisentan and tadalafil resulted in a significantly lower risk of clinical-failure events than the risk with ambrisentan or tadalafil monotherapy.

FUNDING: Gilead Sciences and GlaxoSmithKline

McLaughlin V, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J*. 2015; 46:405-413. DOI: 10.1183/13993003.02044-2014

The safety and efficacy of adding bosentan to sildenafil in pulmonary arterial hypertension (PAH) patients was investigated. In this prospective, double-blind, event-driven trial, symptomatic PAH patients receiving stable sildenafil (≥20 mg three times daily) for ≥3 months were randomized (1:1) to placebo or bosentan (125 mg twice daily). The composite primary end-point was the time to the first morbidity/mortality event, defined as all-cause death, hospitalization for PAH worsening or intravenous prostanoid initiation, atrial septostomy, lung transplant, or PAH worsening. Secondary/exploratory end-points included change in 6-min walk distance and World Health Organization functional class at 16 weeks, change in N-terminal pro-brain natriuretic peptide (NT-proBNP) over time, and all-cause death. Overall, 334 PAH patients were randomized to placebo (n=175) or bosentan (n=159). A primary endpoint event occurred in 51.4% of patients randomized to placebo and 42.8% to bosentan (hazard ratio 0.83, 97.31% CI 0.58–1.19; p=0.2508). The mean between-treatment difference in 6-min walk distance at 16 weeks was +21.8 m (95% CI +5.9–37.8 m; p=0.0106). Except for NT-proBNP, no difference was observed for any other end-point. The safety profile of bosentan added to sildenafil was consistent with the known bosentan safety profile. In COMPASS-2, adding bosentan to stable sildenafil therapy was not superior to sildenafil monotherapy in delaying the time to the first morbidity/mortality event.

FUNDING: Actelion Pharmaceuticals

Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use UPTRAVI® safely and effectively. See full prescribing information for UPTRAVI®.

UPTRAVI® (selexipag) tablets, for oral use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------

UPTRAVI® is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Starting dose: 200 mcg twice daily. (2.1)
- Increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily. (2.1)
- Maintenance dose is determined by tolerability. (2.1)
- Moderate hepatic impairment: Starting dose 200 mcg once daily, increase the dose by 200 mcg once daily at weekly intervals to the highest tolerated dose up to 1600 mcg. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

Pulmonary edema in patients with pulmonary veno-occlusive disease. If confirmed, discontinue treatment. (5.1)

----------ADVERSE REACTIONS----------

Adverse reactions occurring more frequently (≥5%) on UPTRAVI compared to placebo are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Strong CYP2C8 inhibitors: increased exposure to selexipag and its active metabolite. Avoid concomitant use. (7.1, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: discontinue UPTRAVI or breastfeeding. (8.2)
- Severe hepatic impairment: Avoid use. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2015

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2015

1 exp Hypertension, Pulmonary/ 17423
2 sildenafil.mp. 5576
3 bosentan.mp. 1974
4 treprostinil.mp. 328
5 exp Iloprost/ 1099
6 exp Epoprostenol/ 3824
7 tadalafil.mp. 1313
8 riociguat.mp. 86
9 ambrisentan.mp. 223
10 macitentan.mp. 77
11 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12471
12 1 and 11 2694
13 limit 12 to (english language and yr="2014 -Current" and (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 reviews)) 47

Author: Andrew Gibler, Pharm.D.

Date: March 2016

Oral/Inhaled Pulmonary Arterial Hypertension Agents

Goals:

- Restrict use to patients with pulmonary arterial hypertension (PAH) 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 is the diagnosis?	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 for medical appropriateness.
4. Is there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1)?	**Yes:** Go to #8	**No:** Go to #5
5. Is there a diagnosis of chronic thromboembolic pulmonary	**Yes:** Go to #6	**No:** Go to #10

hypertension (WHO Group 4)?		
6. Is the request for riociguat (Adempas®)?	**Yes:** Go to #7	**No:** Go to #10
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 for medical appropriateness.
8. Will the prescriber consider a change to a preferred product? Note: preferred products do not require PA or copay.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #9
9. 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 for medical appropriateness.
10. RPh Only: Prescriber must provide supporting literature for use.	**Yes:** Approve for length of treatment.	**No:** Deny, not funded by the OHP

P&T/DUR Review: 3/16 (AG); 7/14; 3/14; 2/12; 9/10
Implementation: 5/12; 1/12; 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:

Author: Andrew Gibler, Pharm.D. Date: March 2016

- 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 or copay.	**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)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny for 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 for medical appropriateness.
6. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for medical appropriateness.

P&T / DUR Review: *3/16 (AG); 9/12*
Implementation: *1/1/13*