



Pulmonary Arterial Hypertension (PAH) Agents, Oral and Inhaled Therapeutic Class Review (TCR)

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MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Oral Agents		
ambrisentan (Letairis®) ¹	generic, Gilead	Treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) to improve exercise ability and delay clinical worsening In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability
bosentan (Tracleer®) ²	generic, Actelion	Treatment of PAH (WHO Group I) in patients with WHO Class II to IV symptoms, to improve exercise ability and decrease clinical worsening Treatment of idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR) in pediatric patients age 3 years and older which is expected to result in an improvement in exercise ability
macitentan (Opsumit®) ³	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) to reduce the risks of disease progression and hospitalization for PAH
riociguat (Adempas®) ⁴	Bayer	Persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group IV) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class PAH (WHO Group I) to improve exercise capacity, improve WHO functional class and to delay clinical worsening
selexipag (Uptravi®) ⁵	Actelion	Treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
sildenafil (Revatio®) ⁶	generic, Pfizer	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening
tadalafil (Adcirca®) ⁷	generic, Eli Lilly	Treatment of PAH (WHO Group I) to improve exercise ability
treprostinil (Orenitram®) ⁸	United Therapeutics	Treatment of PAH (WHO Group I) to delay disease progression and to improve exercise capacity
Inhalation Agents		
iloprost (Ventavis®) ⁹	Actelion	Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration
treprostinil (Tyvaso®) ¹⁰	United Therapeutics	Treatment of PAH (WHO Group I) to increase exercise ability Treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

Benefits of bosentan (Tracleer) versus risk of liver injury in WHO Class II should be considered; early liver injury may preclude future use as disease progresses. Adding sildenafil (Revatio) to bosentan (Tracleer) therapy does not result in any beneficial effect on exercise capacity. Studies establishing oral treprostinil (Orenitram) effectiveness included predominantly patients with WHO Functional Class (FC) II–III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64% and 75%, respectively) or PAH associated with connective tissue diseases (32% and 19%, respectively). Studies establishing ambrisentan (Letairis) effectiveness included predominately patients with WHO FC II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%). Studies establishing bosentan (Tracleer) effectiveness included predominately patients with NYHA Functional Class II–IV symptoms and etiologies of idiopathic or heritable PAH (60%),

PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Studies establishing macitentan (Opsumit) effectiveness included predominately patients with WHO FC II–IV symptoms and etiologies of idiopathic or heritable PAH (57%), PAH associated with connective tissue disorders (31%), and PAH associated with congenital heart disease with repaired shunts (8%). Studies establishing riociguat (Adempas) effectiveness included predominately patients with WHO FC II–III symptoms and etiologies of idiopathic (61%) or familial PAH (2%), PAH associated with connective tissue disease (25%), and PAH associated with congenital heart disease (8%). Studies establishing selexipag (Upravi) effectiveness included predominately patients with WHO FC II–III symptoms and etiologies of idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%). Studies establishing sildenafil (Revatio) effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%). Studies establishing tadalafil (Adcirca) effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%). Studies establishing iloprost (Ventavis) effectiveness included predominately patients with NYHA Functional Class III–IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%). Studies establishing inhaled treprostinil (Tyvaso) effectiveness for PAH included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%), and studies establishing effectiveness for PH-ILD predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

Sildenafil (Viagra®) and tadalafil (Cialis®) are also FDA-approved for erectile dysfunction (ED).

OVERVIEW

Pulmonary hypertension (PH) is characterized by an increase in pulmonary arterial pressure and secondary right ventricular failure. This is defined by the American College of Cardiology (ACC) as a resting mean pulmonary arterial pressure (mPAP) \geq 25 mm Hg.¹¹ Patients with an mPAP between 21 and 24 mm Hg should be carefully followed, particularly if they are at risk for developing PAH (e.g., patients with connective tissue disease [CTD] or who have family members with idiopathic or heritable pulmonary arterial hypertension). Symptoms of PAH include dyspnea, dizziness, syncope, fatigue, edema (peripheral), angina, palpitations, and other symptoms, all of which are exacerbated by exertion. The prevalence varies substantially depending on the type, etiology, and underlying condition; the prevalence is 15 per million people.¹² PH does not have a cure and, if left untreated, PH is a life-threatening disease with poor prognosis. Although the number of approved therapies for PAH has grown in the past years, the prognosis is still poor, with approximately 50% mortality within the first 5 years after diagnosis.¹³ Management of PH should be limited to specialized centers where clinicians are experienced in the evaluation and treatment of patients with PH.¹⁴

The World Health Organization (WHO) classifies PH patients into 5 groups based on etiology. Group I refers to pulmonary arterial hypertension (PAH); the other 4 groups describe PH.¹⁵ Each group has subgroups. Collectively all 5 groups are referred to as PH. In 2013, clinical classifications were updated

to provide the same PH classifications for adult and pediatric patients. In addition, the individual categorization of the persistent PH of neonates (PPHN) was included.¹⁶

There are many causes of PAH including idiopathic or underlying disease and hereditary causes. There are cellular changes in the walls of pulmonary arteries, and it appears that mutations in the bone morphogenetic protein receptor type 2 (BMP2) gene plays a key role in the pathogenesis of heritable PAH.¹⁷ Other etiologies in PAH include drugs and toxins, collagen vascular resistance, human immunodeficiency virus (HIV), portal hypertension, chronic thromboembolism, and congenital heart disease.

Measuring baseline severity in PH is important prior to initiation of therapy since response to therapy is measured as a change from baseline. Since functional and hemodynamic impairment are central in PH, patients' ability to function is measured by determining exercise capacity, which in turn determines the WHO functional class.¹⁸ The WHO FC classifications are class I: no limitation of physical activity; class II: mild limitation of physical activity; class III: marked limitation of physical activity; class IV: inability to perform any physical activity.

The Food and Drug Administration (FDA) approved treatments for PAH include prostacyclin and prostacyclin analogs (intravenous [IV] epoprostenol [Flolan®, Veletri®], oral treprostinil [Orenitram], IV/subcutaneous [SC] treprostinil [Remodulin®], inhaled treprostinil [Tyvaso], and inhaled iloprost [Ventavis]), an oral prostacyclin receptor agonist (selexipag [Uptravi]), oral endothelin receptor antagonists (bosentan [Tracleer], macitentan [Opsumit], and ambrisentan [Letairis]), oral soluble guanylate cyclase stimulator (riociguat [Adempas]), and oral phosphodiesterase 5 (PDE-5) inhibitors (sildenafil [Revatio] and tadalafil [Adcirca]). This review will focus on oral medications (ambrisentan, bosentan, macitentan, riociguat, selexipag, sildenafil, tadalafil, and treprostinil) and inhaled medications (iloprost and treprostinil) for the treatment of PAH.

In 2019, the American College of Chest Physicians (CHEST) updated their 2014 guidelines on therapy for pulmonary arterial hypertension in adults.¹⁹ This document incorporates recommendations based on recently published clinical trials and expert opinion. The following is a summary of the evidence-based PAH treatment algorithm published by CHEST.

- At the time of diagnosis of PAH, the suggested initial approach is treatment of contributing causes of PAH (e.g., sleep apnea, systemic hypertension), the adoption of general measures (supervised exercise activity, influenza and pneumonia vaccinations, and avoidance of pregnancy, high altitudes, and non-essential surgery), the initiation of supportive therapy (oxygen therapy if needed to maintain oxygen saturations > 91%), and palliative care (ungraded consensus-based statement [UCBS]).
- Unless there is a contraindication, acute vasoreactivity testing should be performed at a facility with experience in performing and interpreting the test (UCBS). A trial of high dose oral calcium channel blockers (CCB), such as amlodipine, diltiazem, or nifedipine, is recommended in patients with a positive acute vasoreactive test. Furthermore, CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity (UCBS). Patients should be followed closely for response and side effects of therapy. Alternative or additional PAH therapy should be initiated if improvement to WHO FC I or II are not seen after the trial of a CCB.
- In treatment-naive patients who are not candidates for, or who have failed CCB therapy, treatment is based on WHO functional class (UCBS).

- In treatment-naïve patients with WHO FC I, continued monitoring for disease progression is advised (UCBS).
 - In treatment-naïve patients with WHO FC II, initial combination therapy with ambrisentan and tadalafil to improve 6-minute walk distance (6MWD) is suggested (weak recommendation, moderate quality evidence). In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, sildenafil (strong recommendations, low quality evidence for both), bosentan, macitentan, tadalafil, or riociguat (UCBS for all 4 products) is recommended.
 - In treatment-naïve patients with WHO FC III without rapid disease progression or poor prognosis, initial combination therapy with ambrisentan and tadalafil to improve 6MWD is suggested (weak recommendation, moderate quality evidence). In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, bosentan, sildenafil (strong recommendations, low or moderate quality to improve 6MWD for all 3 products), macitentan, tadalafil, or riociguat (UCBS for all 3 products) is recommended.
 - For treatment-naïve patients with WHO FC IV, initial therapy with a parenteral prostanoid agent is recommended (UCBS). In patients who cannot comply with parenteral administration, inhaled prostanoid in combination with an oral endothelin receptor antagonist (ERA) or an oral phosphodiesterase type-5 (PDE-5) inhibitor are alternatives (UCBS).
- In patients who remain symptomatic on an oral ERA or PDE-5 inhibitor, addition of an inhaled prostanoid is suggested; CHEST recommends inhaled treprostinil to improve 6MWD (weak recommendation/low quality evidence) or inhaled iloprost to improve WHO functional class and delay time to clinical worsening (UCBS).
 - In patients with WHO FC III and continued disease progression and/or poor prognosis while on oral mono- or combination therapy, addition of a parenteral or inhaled prostanoid may be considered (UCBS).
 - In patients with WHO FC III with rapid disease progression or poor prognosis, despite oral PAH therapy, addition of a parenteral prostanoid (epoprostenol or treprostinil) is recommended to improve 6MWD (UCBS for both products); although there are no data to support use of inhaled or oral prostanoids in this population, they can be considered for patients who are unable to comply with parenteral therapy.
 - In patients with WHO FC III or IV and an inadequate response to initial therapy with mono- or combination therapy, a second or third class of PAH agents should be added (inhaled treprostinil: strong recommendation, low quality evidence; all other products: UCBS). Lung transplantation may be considered in patients with inadequate response to maximal pharmacotherapy (UCBS).
 - Since the 2014 guidelines were published, oral treprostinil (Orenitram) and selexipag (Uptravi) were FDA approved. While the panel states that these new medications may alter the therapeutic landscape of PAH treatment, it did not provide recommendations for or against their use, due to a lack of sufficient data.

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) include oral selexipag (Uptravi) and oral treprostinil (Orenitram) in their 2015 guidelines for the diagnosis and

treatment of pulmonary hypertension.²⁰ Selexipag is included as an option for monotherapy or in combination with an ERA and/or PDE-5 inhibitor in patients with WHO FC II or III (Class 1, Level B for all). Oral treprostinil is recommended as an option for monotherapy in patients with WHO FC III (Class 2b, Level B). Both agents are recommended only in patients who responded to acute vasoreactivity tests.

The World Symposium on Pulmonary Hypertension is typically held every 5 years and is considered to be the foremost authority on PAH.²¹ The most recent meeting, the Sixth World Symposium, was held in March 2018, and the literature from that symposium references the 2015 ESC/ERS guidance as the recommended treatment algorithms.²²

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare consequence of an acute pulmonary embolism (PE) and a potentially curable cause of PH.²³ Initially electrocardiogram and ventilation/perfusion (V/Q) scan are performed to confirm a diagnosis of CTEPH; a negative V/Q scan typically excludes CTEPH. Computed tomography, magnetic resonance imaging (MRI), or invasive pulmonary angiogram are also employed to confirm CTEPH. Once the diagnosis of CTEPH is made, all patients should receive life-long anticoagulant therapy, unless contraindicated. Surgery is the primary treatment for patients with CTEPH and the only potential for cure. However, medical therapy may be considered in cases deemed non-operable. Intravenous epoprostenol, treprostinil SC, oral sildenafil, bosentan, and riociguat have been studied. Riociguat (Adempas) is the only FDA-approved agent for CTEPH in this review.

Patients with PH due to a chronic lung disease, such as interstitial lung disease, are classified by the WHO as having Group 3 PH.²⁴ Treatment of these patients generally revolves around treating the underlying condition, although limited data have evaluated the role of select agents in this class used as adjunctive therapy with varying results; agents in this class have demonstrated various effects, including benefit, no benefit, and serious adverse events. Treprostinil (Tyvaso) is the only agent in this class approved for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. As this Therapeutic Class Review focuses on the role of these agents for the treatment of PAH, the role of treprostinil for patients with Group 3 PH is addressed only in a limited capacity.

PHARMACOLOGY^{25,26,27,28,29,30,31,32,33,34}

Endothelin receptor antagonists: Endothelin-1 (ET-1) is a neurohormone whose effects are mediated by binding to receptors in the endothelium and vascular smooth muscle. Increased ET-1 concentrations in the plasma and lung tissue occur in patients with PAH. Two receptor subtypes, ET_A and ET_B, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. Bosentan (Tracleer) and macitentan (Opsumit) act as competitive antagonists at the endothelin receptor (ET_A and ET_B) and are known as endothelin (ET-1) receptor antagonists. Macitentan was developed by modifying the structure of bosentan. Ambrisentan (Letairis) is selective at the ET_A receptor. Ambrisentan is a high affinity (K_i=0.011 nM) ET_A receptor antagonist with a high selectivity for the ET_A versus ET_B receptor (> 4000-fold). The clinical impact of high selectivity for ET_A or for dual endothelin blockage is unknown.

Prostacyclin analogues: Iloprost (Ventavis) and treprostinil (Orenitram, Tyvaso) are prostacyclin analogues. Their major pharmacologic actions are direct vasodilation of pulmonary and systemic arterial vascular beds. They also inhibit platelet aggregation.

Prostacyclin receptor agonist: Selexipag (Uptravi) is a prostacyclin receptor agonist that is structurally distinct from prostacyclin. Activation of the prostacyclin receptor produces cyclic adenosine monophosphate, which induces vascular smooth muscle relaxation and produces decreases in vascular pressure and pulmonary vascular resistance and an increase in cardiac index.

PDE-5 inhibitors: sildenafil (Revatio) and tadalafil (Adcirca) inhibit PDE-5 in smooth muscle of pulmonary vasculature where PDE-5 is responsible for the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation; vasodilation in the pulmonary bed and systemic circulation (to a lesser degree) can occur.

Soluble guanylate cyclase: Soluble guanylate cyclase (sGC) is an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). Upon binding of NO, sGC catalyzes the synthesis of the signaling molecule cGMP. Pulmonary hypertension is associated with endothelium dysfunction, impaired synthesis of nitric oxide, and insufficient stimulation of the NO-sGC-cGMP pathway. Riociguat (Adempas) has a dual mechanism of action whereby it sensitizes sGC to endogenous NO by stabilizing the binding of NO with sGC and directly stimulates sGC via a different binding site (independent of NO). Both mechanisms lead to increased generation of cGMP with subsequent vasodilation.

PHARMACOKINETICS^{35,36,37,38,39,40,41,42,43,44}

Drug	Half-life (hours)	Bioavailability (%)	Metabolite	Excretion (%)
Oral Agents				
ambrisentan (Letairis)	9	Unknown	Unknown	Renal: minor Non-Renal: major
bosentan (Tracleer)	5	50	Two inactive and 1 active that contributes 10% to 20% of parent drug activity	Renal: 3 Feces: 97
macitentan (Opsumit)	16 (parent drug) 48 (active metabolite)	Unknown	One active metabolite that contributes approximately 40% of the total pharmacological activity	Renal: 50 Feces: 24
riociguat (Adempas)	12	94	Major metabolite is M1 and is 1/3 to 1/30 as potent as riociguat	Renal: 40 Feces: 53
sildenafil (Revatio)	4 (for parent drug and metabolite)	41	N-desmethyl metabolite (active with <i>in vitro</i> potency of PDE-5–50% of parent drug)	Renal: 13 Feces: 80
selexipag (Uptravi)	0.8 – 2.5	49%	One active metabolite that is 37-fold as potent as the parent drug	Elimination via metabolism
tadalafil (Adcirca)	*15	Unknown	Major metabolite is methylcatechol glucuronide which is considered inactive	Feces: 61 Renal: 36
treprostinil (Orenitram)	4	17	Five inactive metabolites (4 are products of oxidation of the 3- hydroxyoctyl side chain; 1 is a glucuronide conjugated derivative: treprostinil glucuronide)	Feces: 13 Renal: 79
Inhalation Agents				
iloprost (Ventavis)	20 to 30 minutes	Unknown	Main metabolite is tetranor-iloprost (inactive in animal studies)	Feces: 12 Renal: 68
treprostinil (Tyvaso)	4	64 to 72 (dose dependent)	Five inactive metabolites (4 are products of oxidation of the 3- hydroxyoctyl side chain and 1 is a glucuronide conjugated derivative: treprostinil glucuronide)	Feces: 13 Renal: 79

*The half-life of tadalafil is 35 hours in PAH patients not receiving bosentan.

CONTRAINDICATIONS/WARNINGS^{45,46,47,48,49,50,51,52,53,54}

Ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit) and riociguat (Adempas) are contraindicated in pregnancy and carry boxed warnings regarding the likelihood of serious birth defects if used by pregnant women. For female patients of reproductive potential, pregnancy must be excluded before initiating treatment, monthly during treatment, and for one month after treatment discontinuation. Appropriate contraception is required during treatment and for one month after treatment discontinuation, as outlined in the product labeling. Due to the risk of embryofetal toxicity, these agents are available through their respective Risk and Evaluation and Mitigation Strategy (REMS) programs.

Ambrisentan (Letairis) is also contraindicated in patients with idiopathic pulmonary fibrosis (IPF), including IPF patients with pulmonary hypertension (WHO Group 3). This safety information comes after a study comparing ambrisentan to placebo in patients with IPF, with and without pulmonary hypertension (WHO Group 3), was terminated early due to lack of efficacy and increased risk of disease progression or death for patients receiving ambrisentan.

Monthly testing for serum liver enzymes is no longer required for prescribing and distribution of ambrisentan following data from clinical trials showing elevations of liver transaminases similar to placebo. It is recommended to order and review these tests as clinically indicated. Ambrisentan should be discontinued if aminotransferases are greater than 5 times the upper limit of normal (ULN) or if elevations are accompanied by bilirubin greater than 2 times ULN, or by signs or symptoms of liver impairment and other causes are excluded.

Bosentan (Tracleer) has 2 boxed warnings related to potentially serious liver injury and teratogenicity. Bosentan has caused at least 3 times the ULN elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases, warranting serum aminotransferase monitoring. In pediatric patients, bosentan caused at least 3 times the ULN elevation in liver aminotransferases in 2% of patients based on a pooled analysis of 4 studies. Rare cases of unexplained hepatic cirrhosis have been reported after prolonged use (> 12 months) of bosentan in patients with multiple comorbidities on multiple drug therapies. There have also been rare reports of liver failure. Bosentan is not recommended in patients with moderate or severe liver impairment, and initiation should generally be avoided in patients with elevated baseline aminotransferases (> 3 times ULN). Strict adherence to the monthly monitoring schedule for the duration of treatment is required to use bosentan. Concomitant use of bosentan with cyclosporine A or with glyburide is contraindicated due to increased bosentan levels and increased liver enzymes, respectively.

Bosentan can cause hypersensitivity reactions including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), anaphylaxis, rash and angioedema. The use of bosentan is contraindicated in patients who are hypersensitive to the product.

Macitentan and selexipag are contraindicated in patients who have experienced a hypersensitivity reaction to the active ingredient or any component.

If signs of pulmonary edema occur in patients on ambrisentan, bosentan, macitentan (Opsumit), selexipag (Uptravi) or riociguat (Adempas), the possibility of underlying pulmonary veno-occlusive disease should be considered and, if confirmed, the medication discontinued.

Baseline aminotransferase levels should be obtained prior to macitentan therapy. If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin or clinical symptoms of hepatotoxicity, discontinue macitentan with consideration to reinstate therapy if the levels normalize and the patient did not experience clinical symptoms of hepatotoxicity. Postmarketing cases of edema and fluid retention occurring within weeks of starting macitentan have been reported, including cases requiring intervention with a diuretic or hospitalization for decompensated heart failure. Patients with underlying left ventricular dysfunction may be at particular risk for developing significant fluid retention after initiation of ERA treatment. If clinically significant fluid retention develops, evaluate the cause and the possible need to discontinue macitentan.

Other ERAs have caused decreases in hemoglobin concentration and hematocrit and similar decreases were observed with macitentan in clinical trials. These decreases have occurred early and stabilized thereafter. It is not recommended to start patients with severe anemia on macitentan and hemoglobin should be measured at initiation of therapy and repeated as clinically indicated.

The administration of riociguat (Adempas) is contraindicated with concomitant use of specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) and nitrates or nitric oxide donors (such as amyl nitrite) in any form due to an increased risk for hypotension; **it is also contraindicated if concurrently used with other sGC stimulators.** Riociguat should not be administered within 24 hours of sildenafil or 24 hours before or within 48 hours after tadalafil. Riociguat is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP).

Riociguat can cause dizziness. Patients should be aware of how they react to the drug before driving or operating machinery.

Concurrent administration of organic nitrates (nitroglycerin) in any form with sildenafil (Revatio) or tadalafil (Adcirca) is contraindicated as the combination potentiates the hypotensive effects. **Nitrates should not be used within 48 hours of the last tadalafil administration.**

Sildenafil is not recommended in pediatric patients with PAH. The recommendation is based on a long-term clinical pediatric trial which showed that low doses of sildenafil are not effective in improving exercise ability and a high dose of sildenafil is associated with a higher risk of death. Though treatment of PAH with sildenafil in children is not an FDA-approved indication, the recommendation against its use in this patient population has been added due to the study results. Sildenafil is not contraindicated in pediatric patients and can be used as a treatment option if the benefits of its use outweigh the risks.

Sildenafil may cause serious vaso-occlusive crises. The effectiveness of sildenafil in PH secondary to sickle cell anemia has not been established.

In post-marketing experience, there have been cases of sudden decrease or loss of hearing in temporal association with the use of PDE-5 inhibitors like sildenafil (Revatio) and tadalafil (Adcirca). Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported in temporal association with the use of PDE-5 inhibitors, including sildenafil and tadalafil when used to treat erectile dysfunction. An observational study suggests an approximate 2-fold increase in the risk of NAION within 1 to 4 days of using a PDE-5 inhibitor. It is not possible to determine whether these reported events are directly related to the use of the drug, to the patient's underlying risk factors, to a combination of these, or to other factors. Patients should be advised to

seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors.

Angina in patients taking tadalafil indicates the need for immediate medical attention.

Phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil and tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing one of these agents, physicians should carefully consider whether their patients with underlying cardiovascular or vasodilatory disease, autonomic dysfunction, or preexisting hypotension could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of one of these agents is not recommended. The use of sildenafil or tadalafil with alpha blockers, blood pressure medications, and alcohol may also lower blood pressure significantly and may lead to symptomatic hypotension (fainting).

The use of selexipag (Uptravi) is contraindicated in patients with concomitant use with strong inhibitors of CYP2C8 (e.g., gemfibrozil).

Inhaled iloprost (Ventavis) has not been evaluated in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease [COPD]) or with acute pulmonary infections. Such patients should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

Inhaled iloprost can cause symptomatic hypotension in patients with low systemic arterial pressure. Inhaled iloprost inhibits platelet aggregation and may lead to an increased risk of bleeding, particularly among patients receiving anticoagulation. If signs of pulmonary edema occur when inhaled iloprost is administered in patients with PH, the treatment should be stopped immediately. This may be a sign of pulmonary venous hypertension. Monitor vital signs while initiating iloprost. It should not be initiated in patients with systolic blood pressure below 85 mm Hg.

Iloprost inhalation can induce bronchospasm which can be more severe or frequent in patients with a history of hyperreactive airways. Iloprost has not been evaluated in patients with COPD, severe asthma, or with acute pulmonary infections. Iloprost has not been studied in patients with pulmonary hypertension and hepatic or renal impairment, both of which increase mean AUC in otherwise normal subjects. Avoid contact of iloprost solution with the skin or eyes; avoid ingestion of the solution.

The efficacy of treprostinil has not been established in patients with significant underlying lung disease such as asthma or COPD. Treprostinil should be titrated slowly in patients with hepatic or renal insufficiency because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

Oral treprostinil (Orenitram) use is contraindicated in patients with severe hepatic impairment (Child Pugh Class C) and its use should be avoided in patients with moderate hepatic impairment (Child Pugh Class B).

Treprostinil also inhibits platelet aggregation and leads to an increased risk of bleeding, particularly in patients receiving anticoagulants. Treprostinil may cause symptomatic hypotension in patients with low systemic arterial pressure.

Administration of oral treprostinil with alcohol may result in a faster rate of tablet dissolution than intended. In addition, the tablet shell does not dissolve and can lodge in a diverticulum in patients with diverticulosis.

Patients with phenylketonuria should be aware that bosentan (Tracleer) 32 mg tablets for oral suspension contain phenylalanine, a component of aspartame.

Risk Evaluation and Mitigation Strategy (REMS)⁵⁵

Ambrisentan (Letairis) products have a shared REMS program to mitigate the risk of embryofetal toxicity. Macitentan (Opsumit) and riociguat (Adempas) products each also have a REMS program to mitigate the risk of embryofetal toxicity. As described in the elements to ensure safe use, all female patients, prescribers, and dispensing pharmacies must be enrolled in the respective REMS program.

Bosentan (Tracleer) products have a shared REMS program to mitigate the risk of hepatotoxicity and embryofetal toxicity. As described in the elements to ensure safe use, all patients, prescribers, and dispensing pharmacies must be enrolled in the Bosentan REMS program.

DRUG INTERACTIONS^{56,57,58,59,60,61,62,63,64,65}

Ambrisentan (Letairis) is metabolized by CYP450 3A, 2C19, uridine 5'-diphosphate glucuronosyltransferases (UGTs), 1A9S, 2B7S, and 1A3S. Ambrisentan is a substrate of the Organic Anion Transport Protein (OATP), and a substrate, but not an inhibitor, of P glycoprotein (P-gp). Drug interactions might be expected because of these factors; however, a clinically relevant interaction has been demonstrated only with cyclosporine. Coadministration of ambrisentan and cyclosporine results in about 2-fold increased ambrisentan exposure; a decreased dose to ambrisentan 5 mg once daily is recommended.

Bosentan (Tracleer) is metabolized by and an inducer of CYP450 2C9 and 3A4, consequently plasma concentrations of drugs metabolized by these 2 isozymes will be decreased when bosentan is co-administered. Concomitant administration of both a CYP2C9 inhibitor (e.g., fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan and is therefore not recommended. The concomitant administration of bosentan and cyclosporine or glyburide is contraindicated. The dose of bosentan should be adjusted when initiating lopinavir/ritonavir or other ritonavir-containing regimens for HIV.

Macitentan (Opsumit) is a CYP3A4 substrate. Strong inducers of CYP3A4 significantly reduce macitentan levels and concomitant use should be avoided. Strong inhibitors of CYP3A4 significantly increase macitentan levels and concomitant use should be avoided.

Riociguat (Adempas) is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of riociguat with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated. Concomitant administration of riociguat with PDE inhibitors, including specific PDE-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) or nonspecific PDE inhibitors (e.g., dipyridamole or theophylline) is contraindicated, due to the risk of hypotension. **It is also contraindicated if concurrently used with sGC stimulators.** Riociguat should not be administered within 24 hours of sildenafil or 24 hours before or within 48 hours after tadalafil.

Advise patients against taking an antacid within 1 hour of riociguat dose.

For patients receiving strong cytochrome P450 (CYP) and P-gp/BCRP inhibitors, such as azole antimycotics (e.g., ketoconazole, itraconazole) or HIV protease inhibitors (e.g., ritonavir), consider a riociguat starting dose of 0.5 mg three times a day. Monitor for hypotension. Strong CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered.

Selexipag (Uptravi) and its active metabolite both undergo oxidative metabolism by CYP2C8. Concomitant administration with strong inhibitors of CYP2C8 may result in a significant increase in exposure to selexipag and its active metabolite. Concomitant administration of selexipag with strong inhibitors of CYP2C8 (e.g., gemfibrozil) is contraindicated. Reduce the dosing frequency of selexipag to once daily when co-administered with a moderate CYP2C8 inhibitor (e.g., clopidogrel, deferasirox, teriflunomide) and revert back to twice daily dosing when co-administration with the moderate CYP2C8 inhibitor is stopped. Concurrent use of selexipag with an inducer of CYP2C8 and UGT1A3/2B7 enzymes (e.g., rifampin) may reduce the exposure to the active metabolite necessitating a dose reduction of selexipag.

Sildenafil (Revatio) is metabolized through the CYP450 3A4 (major) and 2C9 (minor) isoenzyme systems. The use of sildenafil with ritonavir and other potent CYP3A inhibitors is not recommended.

Tadalafil is a substrate of and predominantly metabolized by CYP450 3A. In patients taking potent CYP3A inhibitors (e.g., ketoconazole, itraconazole), avoid concomitant use. The dose of ritonavir should be adjusted if given with tadalafil. Patients on chronic potent inducers of CYP3A (e.g., rifampin) should avoid tadalafil.

The concomitant use of PDE-5 inhibitors (sildenafil and tadalafil) with nitrates in any form is contraindicated. Also, there is a blood pressure lowering effect with concomitant PDE-5 inhibitor and alpha-blocker use.

Drug interaction studies have not been conducted with inhaled treprostinil (Tyvaso). However, there are some studies for the oral (Orenitram) and SC (Remodulin) formulations of treprostinil. Concomitant treprostinil with diuretics, antihypertensives, or other vasodilators may increase the risk of systemic hypotension. Treprostinil dosage adjustments may be necessary if inhibitors or inducers of CYP2C8, such as gemfibrozil and rifampin respectively, are added or withdrawn. Do not mix treprostinil inhalation with other medications in the Optineb[®]-ir device; compatibility of treprostinil with other medications has not been studied.

Although clinical studies have not been conducted, *in vitro* studies of iloprost (Ventavis) indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected. Concomitant iloprost with antihypertensives or other vasodilators may increase the risk of systemic hypotension. Direct mixing of iloprost with other medications in the I-neb[®] AAD[®] System or the Prodose[®] AAD[®] System has not been evaluated; therefore, do not mix with other medications.

Both treprostinil and iloprost inhibit platelet aggregation, so there may be an increased risk of bleeding, particularly among patients receiving anticoagulation.

ADVERSE EFFECTS^{66,67,68,69,70,71,72,73,74,75}

Drug	Epistaxis	Head-ache	Dyspepsia	Flushing	Insomnia	Erythema	Elevations in ALT/AST (> 3X ULN)
Oral Agents							
ambrisentan (Letairis)	nr	15 (14)	nr	4 (1)	nr	nr	0
bosentan (Tracleer)	nr	22 (20)	4 (0)	9 (5)	nr	nr	11 (2)
macitentan (Opsumit)	nr	14 (9)	nr	nr	nr	nr	3.4 (4.5)
riociguat (Adempas)	nr	27 (18)	21 (8)	nr	nr	nr	nr
selexipag (Uptravi)	nr	65 (32)	nr	12 (5)	nr	nr	nr
sildenafil 20 mg three times daily (Revatio) n=69 (placebo n=70)	9 (1)	46 (39)	13 (7)	10 (4)	7 (1)	6 (1)	nr
tadalafil 40 mg/day (Adcirca) n=79 (placebo n=82)	nr	42 (15)	10 (2)	13 (2)	nr	nr	nr
treprostinil* (Orenitram) n=151 (placebo n=77)	nr	63 (19)	reported	15 (6)	nr	nr	nr
treprostinil† (Orenitram) n=346 (placebo n=344)	nr	75 (35)	reported	45 (8)	nr	nr	nr
Inhalation Agents							
iloprost (Ventavis) n=101 (placebo n=102)	39 (26)	27 (9)	30 (20)	12 (3)	13 (8)	8 (5)	nr
treprostinil (Tyvaso)‡ n=115 (placebo n=120)	reported	41 (23)	nr	15 (<1)	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

* Study conducted in patients with no background vasodilator.

† Study conducted in patients with a single background PAH therapy.

‡ Adverse reactions were similar for both PAH and PA-ILD.

As with other PDE-5 inhibitors, there have been rare reports of priapism related to sildenafil and tadalafil therapy.

Reduced sperm counts, which may impair a man's ability to father children, have been observed in patients taking endothelin receptor antagonists (ERAs).

Decreases in hemoglobin and hematocrit have been reported with the use of endothelin receptor antagonists, including bosentan, macitentan, and ambrisentan; therefore, hemoglobin levels should be monitored. Peripheral edema is a known clinical consequence of PAH, and worsening PAH is also a known effect of endothelin receptor antagonists, including bosentan, macitentan, and ambrisentan.

Serious adverse events reported with the use of inhaled iloprost (Ventavis) include congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, kidney failure, hemoptysis, and pneumonia.

Common adverse events reported with use of oral treprostinil (Orenitram) and more frequently than placebo, in a study conducted in patients with no background vasodilator, included diarrhea (30% versus 16%), nausea (30% versus 18%), pain in extremity (14% versus 8%), and jaw pain (11% versus 4%). Common adverse events occurring with oral treprostinil and more frequently than placebo, in a study conducted in patients with a single background PAH therapy, included diarrhea (69% versus 29%), nausea (40% versus 23%), pain in extremity (18% versus 9%), and jaw pain (18% versus 3%). The most common adverse events reported with inhaled treprostinil and more frequently than placebo (Tyvaso) are cough (54% versus 29%) and throat irritation (41% versus 23%). Jaw pain was also reported with the treprostinil via the inhalation route. Serious adverse events reported with the use of inhaled treprostinil include pneumonia and hemoptysis. Post-marketing adverse reactions identified with the use of oral treprostinil include dizziness, dyspepsia, vomiting, myalgia, and arthralgia.

Inhaled treprostinil (Tyvaso) was associated with a higher rate of cough, throat irritation, nasal discomfort, and hemoptysis in a prospective, observational study comparing patients taking inhaled treprostinil and a control group.

SPECIAL POPULATIONS^{76,77,78,79,80,81,82,83,84,85}

Pediatrics

Safety and efficacy of ambrisentan (Letairis), macitentan (Opsumit), riociguat (Adempas), selexipag (Uptravi), sildenafil (Revatio), tadalafil (Adcirca), iloprost (Ventavis), or treprostinil (Orenitram, Tyvaso) have not been established in pediatric pulmonary hypertension patients.

The safety and efficacy of bosentan (Tracleer) has been established in patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

Pregnancy

Previously categorized as Pregnancy Category X, ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), and riociguat (Adempas) labels have been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR); these agents are contraindicated during pregnancy due to risk of miscarriage and/or embryofetal toxicity. Pregnancy must be excluded before starting and during therapy with these products and prevented thereafter using reliable methods of birth control.

Tadalafil (Adcirca) are categorized as Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women. Previously categorized as Pregnancy Category B, sildenafil's (Revatio) labeling has been updated to comply with the PLLR and now advises that there are limited data on use in pregnant women, however case reports and animal studies do not report a clear association with

sildenafil and adverse maternal or fetal outcomes. Furthermore, untreated PAH can lead to risks to the mother and fetus.

Iloprost (Ventavis), oral treprostinil (Orenitram), and inhaled treprostinil (Tyvaso) labeling were updated to comply with the PLLR. There are no adequate and well controlled trials conducted with these products in pregnant women. Some animal studies with iloprost given at twice the recommended human dose demonstrated adverse developmental outcomes. Animal studies using higher than recommended human doses of treprostinil, given by subcutaneous (SC) and oral routes, resulted in decreased pregnancy rate, increased post-implantation loss, decreased fetal viability and growth, soft tissue and skeletal abnormalities.

No adequate or well-controlled studies with selexipag (Uptravi) in pregnant women exist. Animal reproductive studies performed with selexipag showed no clinically relevant effects on embryofetal development and survival.

Renal Impairment

No dosage adjustments are recommended for ambrisentan (Letairis) in patients with mild to moderate renal impairment. No dosage adjustments are required for bosentan (Tracleer) or macitentan (Opsumit) in patients with renal impairment.

No dosage adjustments are needed for riociguat (Adempas) or selexipag (Uptravi) in patients with CrCl \geq 15 mL/min. Safety and efficacy has not been established in patients with CrCl $<$ 15 mL/min and the use of riociguat is not recommended in this population.

No dosage adjustments are recommended for sildenafil (Revatio) in renal impairment in patients with PAH. The dose of tadalafil (Adcirca) should be adjusted in mild (51 to 80 mL/min) to moderate impairment (31 to 50 mL). Start dosing with 20 mg daily and increase to 40 mg based on tolerability. It should be avoided in patients with severe renal impairment.

Iloprost (Ventavis) has not been evaluated in subjects with impaired renal function. Dose adjustment is not required in patients not on dialysis. In patients undergoing intermittent dialysis, exposures to intravenous iloprost (AUC_{0-4}) were nearly 5 times higher than in subjects with renal failure not requiring dialysis and subjects with normal renal function.

Treprostinil exposure did not differ significantly in patients with severe renal impairment requiring dialysis compared to healthy individuals, when given a single 1 mg dose of oral treprostinil (Orenitram). However, since treprostinil and its metabolites are excreted mainly through the urinary route, plasma clearance treprostinil may be reduced in patients with renal insufficiency and may increase the risk of dose-dependent adverse reactions.

Hepatic Impairment

Ambrisentan (Letairis) is not recommended in patients with moderate to severe hepatic impairment. There is no information in mild hepatic insufficiency, but exposure to ambrisentan may be increased. Bosentan (Tracleer) should be avoided in patients with PAH who have moderate to severe hepatic impairment (see boxed warning and dosage adjustment and monitoring instructions in the package insert). Use bosentan with caution in patients with mild hepatic impairment.

On the basis of ERA randomized controlled trials, the incidence of elevated liver function tests (LFTs) > 3 times ULN is about 11% with bosentan and 0% with ambrisentan.⁸⁶ These numbers may not be comparable, as the patient populations in the studies varied.

No dosage adjustment is required for macitentan (Opsumit) in patients with hepatic impairment.

No dosage adjustments are recommended for riociguat (Adempas) in patients with mild to moderate hepatic impairment. Safety and efficacy have not been established in patients with severe hepatic impairment (Child Pugh C) and the use of riociguat is not recommended in this patient population.

No dose adjustment is needed for selexipag (Uptravi) in patients with mild hepatic impairment (Child-Pugh class A). A once-daily regimen is recommended in patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. There is no experience with selexipag in patients with severe hepatic impairment (Child-Pugh class C) and use in these patients should be avoided.

No dosage adjustments are recommended for sildenafil (Revatio) in hepatically impaired patients with PAH. The dose of tadalafil (Adcirca) should be adjusted, 20 mg to start, in mild to moderate hepatic impairment (Child-Pugh A or B); it should be avoided in severe hepatic impairment (Child Pugh C).

Hepatic or renal insufficiency may increase exposure to tadalafil and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8, such as gemfibrozil, or inducers, such as rifampin, are added or withdrawn.

Iloprost (Ventavis) has not been evaluated in subjects with impaired hepatic function. A slow up titration is recommended when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Since iloprost elimination is reduced in hepatic insufficiency, consider increasing the dosing interval (e.g., 3 to 4 hours between doses based on the patient's response at the end of the dose interval), in patients with Child Pugh Class B or C hepatic impairment.

A reduced starting dose of oral treprostinil (Orenitram) at 0.125 mg twice daily is recommended in patients with mild hepatic impairment or on a strong CYP28C inhibitor (e.g., gemfibrozil). Use of oral treprostinil should be avoided in those with moderate hepatic impairment, and its use is contraindicated in those with severe impairment.

Geriatric Patients

In the clinical studies of tadalafil (Adcirca) for pulmonary arterial hypertension, 28% were 65 years of age and over, while 8% were 75 years of age and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

In the 2 placebo-controlled clinical studies of ambrisentan (Letairis), 21% of patients were ≥ 65 years old and 5% were ≥ 75 years old. The elderly (age ≥ 65 years) showed less improvement in walk distances with ambrisentan than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

In the clinical study of macitentan (Opsumit) for PAH, 14% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

In the clinical studies of riociguat (Adempas), 23% were ≥ 65 years and 6% were ≥ 75 years. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. Elderly patients showed a higher exposure to riociguat.

In the clinical studies of selexipag (Uptravi), 18% were 65 years of age and older, 1% were 75 and older. No overall differences were observed between these subjects and younger subjects, but greater sensitivity cannot be ruled out.

Clinical studies of bosentan (Tracleer), sildenafil (Revatio), iloprost (Ventavis), and treprostinil (Tyvaso) did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In patients aged 65 and older receiving oral treprostinil (Orenitram), a slightly greater absolute and relative adverse event rate was reported compared to younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Smokers

Plasma concentration of riociguat (Adempas) are reduced by 50% to 60% in patients who smoke; higher doses may be considered in this population.

DOSAGES^{87,88,89,90,91,92,93,94,95,96}

Drug	Initial Dose	Maximum Daily Dose	How Supplied
Oral Agents			
ambrisentan (Letairis)	5 mg once daily with or without food	10 mg once daily	5 mg, 10 mg tablets
bosentan (Tracleer)	≤ 12 years of age: ≥ 4 - 8 kg; 16 mg twice daily, > 8 – 16 kg; 32 mg twice daily, > 16 – 24 kg; 48 mg twice daily, > 24 – 40 kg; 64 mg twice daily ≥ 12 years of age: 62.5 mg twice daily for first 4 weeks	≤ 12 years of age: 64 mg twice daily ≥ 12 years of age: 125 mg twice daily	32 mg tablet for oral suspension 62.5 mg, 125 mg tablets
macitentan (Opsumit)	10 mg once daily with or without food	10 mg once daily	10 mg tablets
riociguat (Adempas)	1 mg three times a day with or without food	2.5 mg three times a day	0.5 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg tablets
selexipag (Uptravi)	200 mcg twice daily with or without food When used as an intravenous infusion, dosing is based on oral dosing; see product labeling for additional details	1,600 mcg twice daily	Titration Pack: 200 mcg, 800 mcg tablets 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, 1,600 mcg tablets 1,800 mcg/single-use vial
sildenafil (Revatio)	Oral: 5 mg or 20 mg three times, 4 to 6 hours apart daily Injectable: 2.5 mg or 10 mg three times daily as intravenous bolus	Oral: 20 mg three times daily	20 mg tablet 10 mg/mL oral suspension 10 mg (12.5 mL) single-use vial
tadalafil (Adcirca)	40 mg once daily with or without food	40 mg once daily with or without food	20 mg tablet*
treprostinil (Orenitram)	0.25 mg twice daily with food	Determined by tolerability	0.125 mg, 0.25 mg, 1 mg, 2.5 mg, 5 mg extended-release tablets
Inhalation Agents			
iloprost (Ventavis)	2.5 mcg/dose; if tolerated increase to 5 mcg/dose. Administer 6 to 9 times daily (dosing intervals 2 hours while awake according to individual need and tolerability)	45 mcg (or 5 mcg nine times daily)	10 mcg/mL (30 single use 1 ml ampules) and 20 mcg/mL (30 single use 1 mL ampules) oral inhalation solution
treprostinil (Tyvaso)	18 mcg (3 inhalations) four times daily about 4 hours apart; if 3 inhalations not tolerated reduce to 1 to 2 inhalations as tolerated	54 mcg (or 9 inhalations) four times daily (Increase to 54 mcg in 1 to 2 week intervals)	2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL) oral inhalation solution Starter Kit contains 28 ampules and the Tyvaso Inhalation System Refill Kit contains 28 ampules and administration accessories

* A tadalafil product approved via an Abbreviated New Drug Application (ANDA) from Teva (a branded generic) is marketed under the trade name Alyq™.

Ambrisentan (Letairis) should be initiated at 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either the dose of ambrisentan or tadalafil can be increased, as needed and tolerated, to ambrisentan 10 mg or tadalafil 40 mg. The ambrisentan tablets should not be split, crushed, or chewed.

The initial and maintenance dose of bosentan (Tracleer) is 62.5 mg twice daily in patients with low body weight (< 40 kg) and > 12 years old. The 32 mg oral tablet for suspension should be dispersed in water immediately before administration. If needed, the 32 mg tablet can be divided into halves; however, it should not be divided into quarters. Divided tablets may be stored at room temperature in the open blister for up to 7 days.

Riociguat (Adempas) treatment should be initiated at 1 mg taken 3 times daily. A lower starting dose of 0.5 mg three times daily can be considered for patients who may not tolerate the hypotensive effect of riociguat. The dose of riociguat may be increased by 0.5 mg at intervals of no sooner than 2 weeks apart as tolerated to a maximum of 2.5 mg three times daily if systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension. Riociguat should be reinitiated if the dosage is interrupted for 3 or more days. For patients who are unable to swallow whole tablets, riociguat may be crushed and mixed with water or soft foods (such as applesauce) immediately before administration. Dose greater than 2.5 mg three times a day may be considered, if tolerated, in patients who smoke; a subsequent dose reduction may be required if smoking is ceased.

Dividing the dose of tadalafil (Adcirca) over the course of the day is not recommended.

Sildenafil (Revatio) injection is for the continued treatment of patients with PAH who are currently prescribed oral Revatio and who are temporarily unable to take oral medication. The dose of Revatio injection does not need to be adjusted for body weight.

Selexipag treatment should be initiated at 200 mcg taken twice daily. The dose should be increased at increments of 200 mcg twice daily at weekly intervals, up to a dose of 1,600 mcg twice daily, as tolerated. Tolerability is a class issue. Titration should be individualized to minimize side effects. Patients with issues tolerating selexipag can take it with food. Selexipag tablets should not be split, crushed, or chewed. Selexipag injection should be reserved for patients that are unable to take oral tablets. Administration is twice daily, and the dose of the injection should correlate to the dose of the tablets as outlined in the package insert.

Oral dosages of treprostinil (Orenitram) may be increased in increments of 0.25 mg or 0.5 mg twice daily or 0.125 mg three times daily, not more than every 3 to 4 days, as tolerated, until desired clinical response is achieved. The maximum doses studied of oral treprostinil (Orenitram) were 12 mg twice daily in a 12-week blinded study and 21 mg twice daily in an open-label long-term study. Tolerability is a class issue. Titration should be individualized to minimize side effects. Avoid abrupt discontinuation or sudden large reductions in dose. If a dose is missed, take the missed dose as soon as possible. If 2 or more doses are missed, restart at a lower dose and re-titrate. To transition a patient from subcutaneous treprostinil to oral treprostinil, the dose of the subcutaneous product may be reduced up to 30 ng/kg/min per day while the dose of oral treprostinil is simultaneously increased up to 6 mg per day (or 2 mg three times a day) if tolerated.

Both iloprost (Ventavis) and treprostinil (Tyvaso) formulations for inhalation should be used with their respective devices. These formulations should not be orally ingested. To avoid potential interruptions

in drug delivery because of equipment malfunction, the manufacturer of Tyvaso recommends that patients should have access to a back-up Optineb®-ir device. One ampule of treprostinil (Tyvaso) contains a sufficient volume of medication for all 4 treatment sessions in a single day. The effects diminish over the minimum recommended dosing interval of 4 hours; therefore, treatment timing can be adjusted for planned activities.

Iloprost (Ventavis) is intended to be inhaled using either of 2 pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose® AAD® System. To avoid potential interruptions in drug delivery due to equipment malfunctions, the patient should have easy access to a back-up for both devices. The 20 mcg/mL concentration is intended for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Transitioning patients to the 20 mcg/mL concentration using the I-neb® AAD® System will decrease treatment times. Direct mixing of iloprost with other medications in these delivery devices has not been evaluated.

Patients should be advised that iloprost (Ventavis) should be inhaled at intervals of not less than 2 hours and that the acute benefits may not last 2 hours. Thus, patients may want to adjust times of administration to cover planned activities.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by the manufacturer. Search strategy included the use of ambrisentan, bosentan, macitentan, selexipag, sildenafil, tadalafil, riociguat, inhalation iloprost, and inhalation treprostinil for FDA-approved indication of PAH. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

sildenafil (Revatio) versus placebo

In a randomized, double-blind, placebo-controlled study, 278 patients (277 randomized, 1 patient not treated) with symptomatic PAH received placebo or sildenafil (20, 40, or 80 mg) orally 3 times daily for 12 weeks.⁹⁷ The primary endpoint of distance walked in 6 minutes that increased 45 m (+13%), 46 m (+13.3%), and 50 m (+14.7%) for 20, 40, and 80 mg sildenafil groups, respectively ($p \leq 0.001$). There was no change in the placebo group. Mean pulmonary artery pressure, WHO functional class, and the incidence of clinical worsening were also assessed, but the study was not powered to assess mortality. Mean pulmonary artery pressure decreased 2.1, 2.6, and 4.7 mm Hg in the 20 mg ($p=0.04$), 40 mg ($p=0.01$), and 80 mg ($p<0.001$) sildenafil groups, respectively, compared to an increase of 0.6 mm Hg in placebo. The WHO functional class was improved in the sildenafil groups for the 20 mg, 40 mg, and 80

mg strengths ($p=0.04$, $p=0.01$, and $p<0.001$, respectively). The incidence of clinical worsening did not differ significantly between sildenafil and placebo. Common adverse events included flushing, dyspepsia, and diarrhea in the treatment arm. A total of 222 patients entered a long-term extension study of sildenafil monotherapy and showed a 51 m increase in distance walked in 6 minutes at 1 year. Study doses exceeded FDA labeled doses.

Improvements in exercise tolerance, cardiac index, and quality of life (QOL) were demonstrated in a randomized, double-blind, placebo-controlled, crossover design trial. The evaluation compared the efficacy of sildenafil 25 to 100 mg three times daily to placebo in patients with primary pulmonary hypertension (PPH) over 12 weeks.⁹⁸ The primary endpoint was the change in exercise time on treadmill using the Naughton protocol (a graded exercise evaluation treadmill stress test).⁹⁹ Exercise time increased by 44% from 475 ± 168 seconds at the end of placebo phase to 686 ± 224 seconds at the end of sildenafil phase ($p \leq 0.0001$). Secondary endpoints of cardiac index improved from 2.8 ± 0.9 L/m² to 3.45 ± 1.1 L/m² ($p \leq 0.0001$), whereas pulmonary artery systolic pressure decreased insignificantly from 105.23 ± 17.82 mm Hg to 98.5 ± 24.38 mm Hg. There was significant improvement in the dyspnea and fatigue components of the QOL questionnaire. During the placebo phase, one patient died and another had syncope. There were no significant side effects with sildenafil.

In a randomized, double-blind, placebo-controlled study, 267 PAH (WHO FC I-IV) patients [stabilized on intravenous] epoprostenol, were randomized to placebo or sildenafil (in a fixed titration starting from 20 mg to 40 mg and then 80 mg, three times a day) when used in combination with intravenous epoprostenol.¹⁰⁰ The primary endpoint showed that there was a statistically significant greater increase in 6MWD for sildenafil compared with placebo at week 16. The mean change from baseline at week 16 was 30 m for the sildenafil group compared with 4 m for the placebo group, giving an adjusted treatment difference of 26 m (95% confidence interval [CI], 10.8 to 41.2, $p=0.0009$). Patients in the placebo group were 3 times more likely to experience a clinical worsening event (death, lung transplantation, initiation of bosentan therapy, or clinical deterioration requiring a change in epoprostenol therapy), and sildenafil patients experienced a significant delay in time to clinical worsening compared to placebo ($p=0.0074$).

sildenafil (Revatio) versus bosentan (Tracleer)

In a double-blind trial, 26 patients with PAH (WHO FC III) were randomized to receive sildenafil 50 mg twice daily for 4 weeks then 50 mg three times daily or bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily over 16 weeks. Intention-to-treat analysis showed no significant differences between the 2 treatment groups as both improved right ventricular (RV) mass, 6MWD, and cardiac index.¹⁰¹ Study doses of sildenafil exceeded FDA labeled doses.

bosentan (Tracleer) versus placebo

The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was a 16-week, multicenter, randomized, double-blind, placebo-controlled study evaluating the effect of bosentan, a dual endothelin receptor antagonist, on systemic pulse oximetry (primary safety endpoint) and pulmonary vascular resistance (primary efficacy endpoint) in patients with World Health Organization FC III Eisenmenger syndrome. Hemodynamics was assessed by right- and left-heart catheterization.¹⁰² Eisenmenger syndrome is characterized by the development of pulmonary arterial hypertension with consequent intracardiac right-to-left shunt and hypoxemia in patients with preexisting congenital heart disease. Secondary endpoints included exercise capacity assessed by 6MWD, additional hemodynamic

parameters, functional capacity, and safety. Fifty-four patients were randomized 2:1 to bosentan (n=37) or placebo (n=17) for 16 weeks. The placebo-corrected effect on systemic pulse oximetry was 1% (95% CI, -0.7 to 2.8), demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced pulmonary vascular resistance index (-472 dyne.s.cm⁻⁵; p=0.0383). The mean pulmonary arterial pressure decreased (-5.5 mm Hg; p=0.0363), and the exercise capacity increased (53.1 m; p=0.0079). Four patients discontinued as a result of adverse events, 2 (5%) in the bosentan group and 2 (12%) in the placebo group. Bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation.

The purpose of the study was to investigate the effects of bosentan (125 or 250 mg twice daily) on echocardiographic and Doppler variables in 85 patients with World Health Organization class III or IV PAH.¹⁰³ Patients had primary pulmonary hypertension (84%) or PAH associated with connective tissue disease. Of these, 29 patients received placebo and 56 received bosentan (1:2 randomization). Six-minute walk tests and echocardiograms were performed at baseline and after 16 weeks of treatment. Baseline characteristics were similar in the placebo and bosentan groups, and echocardiographic and Doppler findings were consistent with marked abnormalities of right ventricular (RV) and left ventricular (LV) structure and function that were due to PAH. The treatment effect on 6-minute walking distance was 37 m in favor of bosentan (p=0.036). Treatment effects of bosentan compared with placebo on other parameters were statistically significant. Bosentan improved RV systolic function and LV early diastolic filling and lead to a decrease in RV dilation and an increase in LV size in patients with PAH.

The EARLY trial was a multicenter, double-blind, randomized, placebo-controlled trial of 185 patients with WHO class II PAH to assess the effectiveness of bosentan (n=93) versus placebo (n=92).^{104,105} The primary endpoints were pulmonary vascular resistance (PVR) at month 6 (expressed as a percentage of baseline) and change from baseline in 6MWD.

Compared with placebo, bosentan treatment was associated with a reduced incidence of worsening of at least 1 functional class (3% for bosentan versus 13% for placebo, p=0.03) and improvement in hemodynamic variables (including PVR, p<0.05). The +19 m mean (+14 m median) increase in 6MWD with bosentan versus placebo was not significant (p=0.08). There was a significant delay in time to clinical worsening (first seen primarily as symptomatic progression of PAH) with bosentan compared with placebo (hazard ratio (HR), 0.2; p=0.01); however, patients who had withdrawn for any reason were not included in the analysis. Serious adverse events (e.g., syncope, right ventricular failure) were reported in 12 of the patients in the bosentan group and 8 in the placebo group. This study was funded by the manufacturer of bosentan.

A double-blind, placebo controlled trial randomized 213 patients with severe PAH to bosentan 62.5 mg or placebo, twice daily for 4 weeks, followed by either of 2 doses of bosentan (125 or 250 mg) twice daily for a minimum of 12 weeks.¹⁰⁶ At week 16, patients treated with bosentan had an improved 6-minute walking distance (primary endpoint); the mean difference between the placebo group and the combined bosentan groups was 44 m (95% CI, 21 to 67; p<0.001). Bosentan also improved the secondary endpoints of Borg dyspnea index and WHO functional class and increased the time to clinical worsening.

The efficacy of bosentan in pediatric patients was evaluated in an open-label, uncontrolled study of 19 patients with PAH age 3 to 15 years.¹⁰⁷ Patients had primary pulmonary hypertension (n = 10) or PAH related to congenital heart diseases (n = 9) and were WHO FC II (n = 15) or class III (n = 4) at baseline.

Patients received 12 weeks of therapy at a dose of approximately 2 mg/kg twice daily with the dose adjusted based upon the patient's body weight (corresponding to the recommended adult dose). Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant during the study. Of the 19 patients included in the study, hemodynamics were measured in 17 of the patients. The mean decrease in PVR was 389 dyn·sec·cm⁻⁵, which was similar to the effect seen in adults. Hemodynamic improvements from baseline were similar with or without co-administration of epoprostenol.

ambrisentan (Letairis) versus placebo

ARIES-1 and ARIES-2 were two 12-week, randomized, double-blind, placebo-controlled, multicenter studies conducted in 393 patients with PAH (WHO Group I).^{108,109} The study designs were identical with the exception of the comparative doses used (ARIES-1: ambrisentan 5 mg and 10 mg; ARIES-2: ambrisentan 2.5 mg and 5 mg) and the geographic locations. Both studies allowed the addition of ambrisentan or placebo to current therapy except epoprostenol, treprostinil, iloprost, bosentan, or sildenafil. The primary study endpoint was the 6MWD. Both studies showed that active treatment with ambrisentan resulted in significant improvement in 6MWD and improvements increased with dose ($p < 0.001$). Additionally, time to clinical worsening was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape. Early escape is defined as any 2 of the following: a 20% decrease in the 6MWD; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. There was a significant delay in the time to clinical worsening for patients receiving ambrisentan versus placebo (ARIES-1: 97% versus 89%; $p = 0.03$ and ARIES-2: 94% versus 79%; $p = 0.005$).

Long-term follow-up of ARIES-1, ARIES-2, and ARIES-E (the open-label extension of these studies where 383 patients received ambrisentan 2.5, 5, or 10 mg) was performed.¹¹⁰ After 2 years, mean change from baseline in 6MWD was improved for the 5 mg (+23 m; 95% CI, 9 to 38 m) and 10 mg (+28 m; 95% CI, 11 to 45 m) groups. Estimates of survival and freedom from clinical worsening for the combined dose group were 94% and 83%, respectively, at 1 year and 88% and 72%, respectively, at 2 years. Ambrisentan was generally well tolerated.

ambrisentan (Letairis) versus tadalafil (Adcirca)

AMBITION, a randomized, double-blind, active-control trial conducted in 605 patients with WHO FC II or III PAH were randomized 2:1:1 to once daily ambrisentan plus tadalafil or to ambrisentan or tadalafil alone.¹¹¹ Treatment was initiated with ambrisentan 5 mg and tadalafil 20 mg. If tolerated, tadalafil was increased to 40 mg at 4 weeks and ambrisentan was increased to 10 mg at 8 weeks. The primary endpoint was time to first occurrence of death, hospitalization for worsening PAH, > 15% decrease from baseline in 6MWD combined with WHO FC III or IV symptoms sustained over 14 days (short term clinical worsening), or reduction in 6MWD sustained over 14 days combined with WHO FC III or IV symptoms sustained over 6 months (inadequate long term clinical response). Patients had idiopathic PAH (55%), heritable PAH (3%), or PAH associated with connective tissue diseases, congenital heart disease, stable HIV infection, or drugs or toxins (43%). Median time from diagnosis to first study drug administration was 25 days. Approximately 32% and 68% of patients were in WHO FC II and III, respectively. The mean patient age was 55.7 years (34% were ≥ 65 years old). 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 2 monotherapy groups combined). The hazard ratio for the primary end point in the combination-therapy group versus the pooled-monotherapy group was 0.5 (95% 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 (NT-proBNP) levels than did the pooled-monotherapy group (mean change, -67.2% versus -50.4%; $p < 0.001$), as well as a higher percentage of patients with a satisfactory clinical response (39% versus 29%; odds ratio, 1.56 [95% CI, 1.05 to 2.32]; $P = 0.03$) and a greater improvement in the 6MWD (median change from baseline, 48.98 m versus 23.8 m; $p < 0.001$).

bosentan (Tracleer) and ambrisentan (Letairis)

Due to a lack of other data on survival for agents in this class, this analysis has been included. A retrospective cohort analysis was conducted from 2 double-blind, randomized trials and their open-label extensions, treated with first-line bosentan, with a 3 year follow-up.¹¹² The results suggest that first-line bosentan therapy, followed by the addition of other disease-specific therapies as required, improve survival in patients with advanced PAH. Some uncontrolled observational studies suggest ambrisentan may be a once-daily alternative for patients who have experienced asymptomatic aminotransferase elevations on other endothelin receptor antagonists after aminotransferase levels have returned to normal.^{113,114}

tadalafil (Adcirca) versus placebo

Tadalafil was studied in a 16-week, double-blind, placebo-controlled trial, (Pulmonary Arterial Hypertension and Response to Tadalafil study [PHIRST]), of 405 patients with PAH and either treatment-naïve or on background therapy with bosentan.^{115,116} Of the patients in the study, 53% were receiving concomitant bosentan therapy up to 125 mg twice daily. Chronic anticoagulation was also allowed. Participants were randomized to placebo or tadalafil 2.5, 10, 20, or 40 mg orally once daily. The primary endpoint was the change from baseline to week 16 in the distance walked in 6 minutes. Secondary endpoints included: changes in WHO functional class, clinical worsening, and health-related quality of life. Tadalafil was found to increase the distance walked in 6 minutes. This effect was dose-dependent; only the 40-mg dose met the specified level of statistical significance ($p < 0.01$). Overall, the mean placebo-corrected treatment effect was 33 m (95% CI, 15 to 50 m). The treatment effect was greater in the bosentan-naïve group, with an increase of 44 m (95% CI, 20 to 69 m) compared with 23 m (95% CI, -2 to 48 m) in patients on background bosentan therapy. Tadalafil 40 mg improved the time to clinical worsening ($p = 0.041$), incidence of clinical worsening (68% relative risk reduction; $p = 0.038$), and health-related quality of life. The changes in WHO functional class were not statistically significant.

Tadalafil monotherapy and as add-on to background bosentan were compared in a 16-week randomized double-blind placebo-controlled trial.¹¹⁷ Patients randomized to tadalafil or placebo ($n = 405$) were analyzed by bosentan use (yes= $n = 216$, no= $n = 189$). Treatment differences in 6MWD (placebo-adjusted), functional class, clinical worsening, and adverse events were assessed. At week 16, placebo-adjusted 6MWD increases were 44 m (95% CI, 20 to 69 m; $n = 37$) for tadalafil 40 mg in treatment-naïve patients and 23 m (95% CI, -2 to 48 m; $n = 42$) for tadalafil 40 mg add-on to bosentan. At week 16 compared to baseline, 6MWD for treatment-naïve and background bosentan placebo-controlled patients decreased by 3 m and increased by 19 m, respectively. Five percent of treatment-naïve

patients had clinical worsening with tadalafil 40 mg compared with 22% with the placebo group (HR, 3.3; 95% CI, 1.1 to 10). Five percent on background bosentan patients had clinical worsening with tadalafil 40 mg add-on compared with 11% for placebo add-on (HR, 1.9; 95% CI, 0.4 to 10.2). Adverse events were similar for tadalafil monotherapy and as add-on. The authors concluded that tadalafil provided clinical benefit as monotherapy. Although it was well-tolerated as add-on to background bosentan, data are insufficient to conclude additional benefit.

iloprost (Ventavis) versus placebo

A randomized, double-blind, multicenter, placebo-controlled trial of 203 patients with PAH and chronic thromboembolic PH, FC III or IV, were randomized to inhaled iloprost (2.5 to 5 mcg, 6 to 9 times per day) or placebo for 12 weeks.^{118,119} The primary endpoint was improvement of WHO class and greater than 10% improvement in 6MWD and was greater in the iloprost group versus placebo (17% versus 5%, $p=0.0007$).

iloprost (Ventavis) versus placebo with background bosentan

In a randomized, multicenter, double-blind trial, inhaled iloprost (5 mcg) or placebo was added to stable monotherapy with bosentan for 12 weeks.¹²⁰ Efficacy endpoints included change from baseline in 6MWD, modified NYHA functional class, hemodynamic parameters, and time to clinical worsening. A total of 67 patients with PAH (55% IPAH, 45% associated PAH, 94% NYHA class III, and mean baseline 6MWD of 335 m) were randomized. At Week 12, patients receiving iloprost had a mean increase in 6MWD of 30 m ($p=0.001$); placebo patients had a mean 6MWD increase of 4 m ($p=0.69$), with a placebo-adjusted difference of +26 m ($p=0.051$). NYHA status improved by one class in 34% of iloprost versus 6% in placebo ($p=0.002$). Iloprost delayed the time to clinical worsening ($p=0.0219$). Improvements were noted in post-inhalation placebo-adjusted change in mean pulmonary artery pressure (-8 mm Hg; $p<0.001$) and pulmonary vascular resistance ($p<0.001$). Combination therapy was well tolerated.

treprostinil oral (Orenitram) versus placebo

FREEDOM-C/C2:^{121,122,123} Two 16-week, double-blind, placebo-controlled studies enrolled a total of 660 patients with PAH who were on stable background therapy with an ERA, PDE-5 inhibitor, or both. Patients were in WHO FC II (23%) and FC III (77%) of varied etiologies. Patients were randomized to twice daily oral treprostinil or placebo. In FREEDOM-C, study drug was initiated at 1 mg twice daily; 0.5 and 0.25 mg tablets were introduced at sequentially later dates during the study. In FREEDOM-C2, doses were initiated at 0.25 mg twice daily. In both studies, treprostinil was titrated to a maximum of 16 mg twice daily based on clinical response and tolerability. Median dose at week 16 was 3 mg twice daily in both trials. No significant differences in the primary endpoint of change in 6MWD between treprostinil- and placebo-treated patients were reported in either study. No significant differences were reported in secondary endpoints including time to clinical worsening, change in WHO functional class, Borg dyspnea score, and dyspnea fatigue index score.

FREEDOM-M:^{124,125} A 12-week, double-blind, placebo-controlled trial randomized 349 patients with WHO Group 1 PAH who were not currently receiving PAH therapy to receive oral treprostinil or placebo twice daily. The majority of patients had WHO FC II (33%) and FC III (66%) of varied etiologies. At the beginning of the study, subjects were dosed with only the 1 mg tablets with 0.5 and 0.25 mg tablets introduced at sequentially later dates during the study. The primary analysis population

consisted of the 228 patients who had access to the 0.25 mg tablet at the time of randomization. Study drug was titrated based on clinical response and tolerability. Primary efficacy endpoint in all studies was the placebo-corrected change in 6MWD from baseline to study end. Patients receiving treprostinil improved their median 6MWD by approximately +23 meters ($p=0.013$) as compared to those receiving placebo; median change from baseline was +25 meters and -5 meters, respectively. Change in secondary measures, such as fatigue, shortness of breath, change in WHO functional class, and time to clinical worsening (death, transplant, atrial septostomy, hospitalization, 20% decrease in 6MWD), did not differ between study drug and placebo ($p>0.05$). Mean dose of treprostinil at week 12 was 3.4 mg twice daily. FREEDOM-EXT was a long-term uncontrolled extension of the placebo-controlled studies ($n=824$).¹²⁶

FREEDOM-EV:¹²⁷ An international, multicenter, double-blind, event-driven study that included 690 patients with WHO Group 1 PAH randomized 1:1 to receive oral treprostinil (dose titrated from 0.125 mg three times a day up to a maximum of 12 mg three times a day based on clinical response) or placebo. The primary efficacy endpoint of the study was the time to the first clinical worsening event defined as death, hospitalization due to worsening of PAH, initiation of inhaled/infused prostacyclin, disease progression ($\geq 15\%$ decrease in six minute walk distance [6MWD] and increase in functional class [FC] or worsening heart failure), or unsatisfactory long-term clinical response. At baseline, 72% of patients were receiving either a PDE-5 inhibitor or a soluble guanylate cyclase, and 28% were receiving an ERA alone. Most patients were classified as WHO FC II (63%) with an average 6MWD of 396 (± 96) meters. The majority of patients (63%) had either idiopathic or heritable PAH, or collagen vascular disease association PAH (26%). The primary endpoint of clinical worsening occurred in 26% of the treprostinil group versus 36% of the placebo group demonstrating a significant difference (HR, 0.74; 95% CI, 0.56 to 0.97; $p=0.028$). While the primary endpoint of the study was a composite endpoint, the difference in the groups was primarily driven by the percentage of patients that experienced disease progression, 5.5% of the treprostinil group versus 14.5% of the placebo group (HR, 0.39; 95% CI, 0.23 to 0.66; $p<0.001$).

treprostinil inhalation (Tyvaso) versus placebo

TRIUMPH-1 was a randomized, double-blind, multicenter, 12-week placebo-controlled study of 235 patients with PAH (mostly functional class III) who were receiving either bosentan or sildenafil for at least 3 months prior to study initiation.^{128,129,130} Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or inhaled treprostinil in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82%); bosentan was the concomitant oral medication in 70% of those enrolled; sildenafil in 30%. Patients taking treprostinil in 4 daily inhalation sessions achieved a 20-meter improvement in 6MWD over those taking placebo ($p<0.0005$). The safety and effectiveness in patients with underlying lung disease have not been established.

INCREASE, a 16-week, randomized, double-blind, placebo-controlled, multicenter study ($n=326$), established the safety and effectiveness of inhaled treprostinil for the treatment of PH-ILD, including patients with idiopathic interstitial pneumonia (45%; inclusive of idiopathic pulmonary fibrosis), pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%).^{131,132} Included patients were randomized 1:1 to inhaled treprostinil 4 times daily (target of 54 mcg/session; maximum 72 mcg/session) or placebo. At baseline, the mean 6MWD was 260 m. The primary efficacy

endpoint was the change in 6MWD at 16 weeks. At week 16, the least-squares mean difference (LSMD) in the change from baseline in 6MWD in the treprostinil group compared to the placebo group was 31.12 m (95% CI, 16.85 to 45.39; $p < 0.001$). The effect on 6MWD was found to be consistent across various subgroups assessed (e.g., etiology, severity, age, sex, dose, hemodynamics). Clinical worsening, defined as hospitalization due to a cardiopulmonary indication, decrease in 6MWD > 15% from baseline (2 consecutive visits ≥ 24 hours apart), all-cause death, or lung transplantation, occurred in 22.7% of treprostinil-treated patients compared to 33.1% treated with placebo (HR, 0.61; 95% CI, 0.4 to 0.92). The time to first clinical worsening event was also lower with treprostinil compared to placebo ($p = 0.041$).

macitentan (Opsumit) versus placebo

SERPAHIN:¹³³ The effect of macitentan on progression of PAH was demonstrated in a placebo-controlled, multicenter, event-driven, trial in patients with symptomatic (WHO FC II–IV) PAH confirmed by right heart catheterization. Patients ($n = 742$) were randomized to placebo ($n = 250$), 3 mg macitentan ($n = 250$) (not an FDA-approved strength), or 10 mg macitentan ($n = 242$) once daily. The primary endpoint was time to the first occurrence of death or first event related to PAH defined as atrial septostomy, lung transplantation, initiation of intravenous or subcutaneous prostanoids, or “other worsening of PAH” defined as all 3 of the following occurring: a sustained $\geq 15\%$ decrease from baseline in 6MWD, worsening of PAH symptoms (worsening of WHO functional class), and need for additional treatment for PAH. All “other worsening events” were confirmed by an independent adjudication committee, blinded to treatment allocation. A secondary endpoint was time to PAH death or PAH hospitalization. At baseline, the majority of enrolled patients (64%) were being treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61%) and/or inhaled/oral prostanoids (6%).

A total of 287 patients had a primary endpoint over a median treatment period of 115 weeks: 116 (46.4%) in the placebo group, 95 patients (38%) in the 3 mg group, and 76 patients (31.4%) in the 10 mg group. Treatment with macitentan 10 mg resulted in a 45% reduction (HR, 0.55; 97.5% CI 0.39 to 0.76; log rank $p < 0.0001$) in the occurrence of the primary endpoint. Benefits were shown both for patients who had not received treatment previously and for those receiving background therapy for PAH. The beneficial effect of macitentan 10 mg was primarily attributable to a reduction in clinical worsening events. The risk of PAH-related death or hospitalization for PAH was reduced by 50% in patients receiving macitentan 10 mg compared to placebo (HR, 0.5; 97.5% CI, 0.34 to 0.75; log rank $p < 0.0001$). The number of patients that discontinued the study due to adverse events in placebo, 3 mg macitentan and 10 mg macitentan group were 31 (12.4%), 34 (13.6%), and 26 (10.7%), respectively. A sensitivity analysis was performed to account for premature discontinuation of treatment were consistent with the primary analysis. While no liver toxicity was reported, reduction in blood hemoglobin ≤ 8 g/dL was observed in 4.3% of patients receiving macitentan 10 mg.

riociguat (Adempas) versus placebo

Chronic ThromboEmbolic Pulmonary Hypertension sGC-Stimulator Trial (CHEST-1):¹³⁴ A randomized, double blind, placebo-controlled, multicenter, 16-week, phase 3, manufacturer-funded, trial evaluated the safety and efficacy of riociguat in 261 patients with inoperable or recurrent/persistent Chronic Thromboembolic Pulmonary Hypertension (CTEPH). The primary endpoint was the change from baseline to the end of week 16 in 6MWD. Secondary endpoints included changes from baseline in

pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO functional class, time to clinical worsening, Borg dyspnea score, quality-of-life variables, and safety. In the study, 72% of patients had inoperable CTEPH, 28% had recurrent or persisting pulmonary hypertension following pulmonary endarterectomy. At baseline, the majority of patients had a WHO functional class II (31%) or III (64%). Concomitant therapy with nitric oxide donors, endothelin-receptor antagonists (ERAs), prostacyclin analogues, specific PDE-5 inhibitors, and nonspecific phosphodiesterase inhibitors was not permitted. By week 16, the 6MWD had increased by a mean of 39 m in the riociguat (titrated up to 2.5 mg three times daily) arm, as compared with a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95% CI, 25 to 67; $p < 0.001$). Patients receiving riociguat (83%) experienced an improvement in 6MWD compared to 57% on placebo. There was statistically significant improvement in some of the secondary endpoints. PVR decreased by 226 $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$ in the riociguat group and increased by 23 $\text{dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$ in the placebo group (least-squares mean difference, $-246 \text{ dyn}\cdot\text{sec}\cdot\text{cm}^{-5}$; 95% CI, -303 to -190 ; $p < 0.001$). Riociguat was also associated with significant improvements in NT-proBNP level ($p < 0.001$), and WHO functional class ($p = 0.003$). Two deaths (due to heart failure and acute renal failure) were reported in the riociguat group versus 3 deaths in the placebo arm. Only the case of acute renal failure was considered to be related to riociguat by the investigator. The most common serious adverse events were similar in both groups with right ventricular failure in 3% of patients in each group and syncope in 2% for riociguat versus 3% for placebo. CHEST-2 was an open-label extension study of the CHEST-1 trial.

An open label extension study (CHEST-2) included 237 patients who completed CHEST-1 and assessed the probability of survival for the patients at 1 and 2 years.¹³⁵ With a mean treatment duration of 1,077 days (± 433), the probabilities of survival at 1 and 2 years were 97% and 93%, respectively. However, this study did not include a control group.

Pulmonary Arterial Hypertension sGC-Stimulator Trial (PATENT-1):¹³⁶ A randomized, double-blind, placebo-controlled, multicenter, 12-week, phase 3, manufacturer-funded, study evaluated the safety and efficacy of riociguat in 443 treatment naive or pre-treated PAH patients. Riociguat in individually adjusted doses of up to 2.5 mg three times daily (2.5 mg–maximum group), or riociguat in individually adjusted doses that were capped at 1.5 mg three times daily (1.5 mg–maximum group). The 1.5 mg–maximum group was included for exploratory purposes, and the data from that group were analyzed descriptively. Data for the 2.5 mg–maximum group is reported here. Patients who were receiving no other treatment for PAH and patients who were receiving ERAs or (non-intravenous) prostanoids for 3 months or more were eligible. A total of 50% of the patients were treatment-naïve with respect to PAH therapy, 44% were pre-treated with an ERA and 6% were pre-treated with a prostacyclin analogue (inhaled, oral, or subcutaneous). At baseline, the majority of patients had a WHO functional class II or III. The primary endpoint was the change from baseline to the end of week 12 in the distance walked in 6 minutes (6MWD). Secondary endpoints, which were determined by hierarchical testing, included the change in pulmonary vascular resistance (PVR), NT-proBNP levels, WHO functional class, time to clinical worsening, score on the Borg dyspnea scale, quality-of-life variables, and safety. By week 12, the 6MWD had increased by a mean of 30 m in the 2.5 mg–maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% CI, 20 to 52; $p < 0.001$). Prespecified subgroup analyses showed that riociguat improved the 6MWD both in patients who were receiving no other treatment for the disease (least-squares mean difference, 38 m; 95% CI) and in those who were receiving ERAs or prostanoids (least-squares mean difference, 34 m; 95% CI). There were significant improvements in PVR ($p < 0.001$), NT-proBNP levels ($p < 0.001$), WHO functional class

($p=0.0033$), time to clinical worsening ($p=0.005$), and Borg dyspnea score ($p=0.002$). The increase in exercise capacity was also demonstrated in patients on background therapy. Two deaths (due to sepsis and hemoptysis) were reported in the riociguat 2.5 mg–maximum group versus 4 deaths in the placebo arm. The most common serious adverse event in the riociguat 2.5 mg–maximum group versus the placebo group was syncope (1% versus 4%, respectively). PATENT-2 was an open-label long-term extension study of PATENT-1.

riociguat (Adempas) replacing PDE-5 inhibitor versus continued PDE-5 inhibitor

The Riociguat rEplacing PDE-5 inhibitor therapy evaluated Against Continued PDE-5 inhibitor thErapy (REPLACE) study was a randomized, controlled, multinational, open-label, manufacturer-funded study.¹³⁷ The study included 226 patients (ages 18 to 75 years of age) with symptomatic PAH at intermediate risk of 1-year mortality (based on the ESC/ERS guideline thresholds for WHO functional class and ≤ 6 MWD) who were receiving treatment with a PDE-5 inhibitor, with or without an ERA for ≥ 6 weeks before randomization. Patients were excluded if they had been previously treated with riociguat, had used prostacyclin analogues or prostacyclin receptor agonists within 30 days before randomization, had clinically significant restrictive or obstructive parenchymal lung disease, or had left heart disease. Patients were randomized to oral sildenafil or tadalafil or to switch to riociguat. The primary endpoint was clinical improvement by week 24 in 2 of 3 variables (6MWD, WHO functional class, and NT-proBNP). Clinical improvement was seen in 45 of 111 patients (41%) in the riociguat arm compared to 23 of 113 patients (20%) in the PDE-5 inhibitor arm (odds ratio, 2.78; 95% CI, 1.53 to 5.06; $p=0.0007$). The most frequently occurring adverse events were hypotension (14%), headache (13%), and dyspepsia (9%) in the riociguat group, and headache (7%), cough (6%), and upper respiratory tract infection (6%) in the PDE-5 inhibitor group. Serious adverse events were reported in 7% in the riociguat group compared to 17% of patients in the PDE-5 inhibitor group; 4 patients died in the PDE-5 inhibitor group.

selexipag (Uptravi) versus placebo

The Prostacyclin (PGI₂) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study: a double-blind, randomized, parallel-group, placebo-controlled, event-driven, phase 3, multicenter, study investigating the safety and efficacy of selexipag in patients with PAH who were not receiving therapy at baseline and those who were already receiving 1 or 2 therapies for the disease at baseline (not including prostacyclin analogs).¹³⁸ The study included 1,156 patients (18 to 75 years of age) who had idiopathic (56.1%), or heritable (2.2%) or PAH associated with HIV infection (0.9%), drug use or toxin exposure (2.3%), connective tissue disease (28.9%), or repaired congenital systemic-to-pulmonary shunts (9.5%). At baseline, the majority of patients had a WHO functional class II (45.8%) or III (52.5%) and were being treated with a stable dose of an endothelin receptor antagonist (ERA) (14.7%), a PDE-5 inhibitor (32.4%), or both (32.5%). The trial also included patients who were not receiving any other PAH treatment prior to enrollment (20.4%). Patients entered the trial in a 12-week adjustment phase. During this phase, selexipag was initiated at a dose of 200 mcg twice daily and was increased until unmanageable side effects occurred, at which point the dose was decreased to what was considered the maximum tolerated dose for the patient. After the adjustment phase, patients entered the maintenance phase where the dose could be titrated up or down. The maximum dose allowed was 1,600 mcg twice daily. The primary endpoint was a composite of death from any cause or a complication related to PAH up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo). Secondary endpoints included the

change in the 6MWD from baseline to week 26 (measured at trough levels of the study drug), the absence of worsening of WHO functional class from baseline to week 26, death due to PAH or hospitalization for worsening of PAH up to the end of treatment period, and death from any cause up to the end of the study. By the end of the study, 155 patients (27%) in the selexipag group and 242 patients (41.6%) in the placebo group experienced a primary endpoint event. The hazard ratio for a primary endpoint event in the selexipag group was 0.6 (99% CI, 0.46 to 0.78; $p < 0.001$). Disease progression and hospitalization accounted for 81.9% of the events. Regarding the secondary endpoints of death due to PAH or hospitalization for worsening of PAH up to the end of the treatment period, 102 selexipag patients (17.8%) and 137 placebo patients (23.5%) experienced an event ($p = 0.003$). For the secondary endpoint of death up to the end of the study, 70 selexipag patients (12.2%) and 83 placebo patients (14.3%) experienced death due to PAH ($p = 0.18$), 100 selexipag patients (17.4%) and 105 placebo patients (18%) experienced death from any cause ($p = 0.42$). Most of the patients in the study experienced at least 1 adverse event (559 patients [96.9%] in the placebo group and 565 patients [98.3%] in the selexipag group). Overall, 41 patients (7.1%) in the placebo group and 82 patients (14.3%) in the selexipag group discontinued their study regimen prematurely because of an adverse event. The most frequent adverse events leading to discontinuation in the selexipag group (with a 1% or greater difference between the selexipag and placebo groups) were headache (3.3%), diarrhea (2.3%), and nausea (1.7%). The most frequently experienced adverse events in the selexipag group reported in more than 20% of patients include headache (375 patients [65.2%]), diarrhea (244 patients [42.4%]), nausea (193 patients [33.6%]), jaw pain (148 patients [25.7%]), and worsening of PAH (126 patients [21.9%]). Hyperthyroidism occurred in 8 patients in the selexipag group and led to treatment discontinuation in 1 patient. No serious adverse events were reported more frequently (at a rate >1% higher) in the selexipag group than in the placebo group. Adverse reactions were more frequent during the dose titration phase.

META-ANALYSES

A meta-analysis of 21 randomized controlled PAH trials reported that therapy with a prostanoid, an ERA, or a PDE-5 inhibitor improves mortality compared to placebo (1.5% versus 3.8%, relative risk [RR], 0.57; 95% CI, 0.35 to 0.92).¹³⁹ The average duration of the trials was 14.3 weeks.

A systematic review and meta-analysis through November 2009 included 3,758 patients.¹⁴⁰ Data was pooled for 3 classes of medications: prostanoids, endothelin-receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE-5) inhibitors. Pooled relative risks (RRs) and 95% confidence intervals were calculated for mortality, 6MWD, dyspnea scores, hemodynamic parameters, and adverse effects. Mortality in the control arms was a combined 4.2% over the mean study length of 14.9 weeks. There was significant mortality benefit with prostanoid treatment (RR, 0.49; 95% CI, 0.29 to 0.82), particularly comparing intravenous agents to control (RR 0.3; 95% CI, 0.14 to 0.63). Mortality benefit was not observed for ERAs (RR, 0.58; 95% CI, 0.21 to 1.6) or PDE-5 inhibitors (RR, 0.3; 95% CI, 0.08 to 1.08). All 3 classes of medication improved other clinical and hemodynamic endpoints. Adverse effects that were increased in treatment arms include jaw pain, diarrhea, peripheral edema, headache, and nausea in prostanoids; and visual disturbance, dyspepsia, flushing, headache, and limb pain in PDE-5 inhibitors. No adverse events were significantly associated with ERA treatment.

The pooled effect of a systematic review of all PAH clinical trials, produced a significant all-cause mortality reduction: 39% (95% CI, 2 to 62, $p = 0.041$).¹⁴¹ This reduction only applied to patients with advanced disease for 16 weeks. Individual drug classes did not produce a statistically significant

reduction in all-cause mortality. Mechanism of mortality reduction unclear but not related to specific drug class, dose, or drug effects on 6MWD, or hemodynamics.

A Cochrane review of 36 studies of ≥ 12 weeks in treatment duration of PDE-5 inhibitors for all-cause PH found that these agents have a benefit in patients with Group 1 PAH (19 studies).¹⁴² Compared to placebo, those treated with a PDE-5 inhibitor were more likely to improve their WHO FC (odds ratio [OR], 8.59; 95% CI, 3.95 to 18.72) and walk 48 meters further in the 6MWD (95% CI, 40 to 56). In addition, they were 22% less likely to die over a mean of 14 weeks (95% CI, 0.07 to 0.68); however, adverse effects were higher with a PDE-5 inhibitor compared to placebo. Data were limited for other comparisons (e.g., combination versus monotherapy, PDE-5 inhibitor versus other PAH treatments, within group comparisons of PDE-5 inhibitors); while some additional results were presented, they are limited by the quantity and heterogeneity of supporting evidence. The authors concluded that choice of PDE-5 inhibitor should be based on the adverse effect profile for each patient.

A MEDLINE, Cochrane, and the International Clinical Trial Registry Platform review evaluated 7 studies focused on the effect of an endothelin receptor antagonist and PDE-5 inhibitor combination in pulmonary arterial hypertension on the difference in clinical worsening, 6MWD, pulmonary vascular resistance, and NT-proBNP between the groups.¹⁴³ Endothelin receptor antagonist and PDE-5 inhibitor combination therapy demonstrated significantly improved 6MWD (mean difference, 15.64 m; 95% CI, 2.67 to 28.61; $p=0.02$), clinical worsening (OR, 0.56; 95% CI, 0.41 to 0.76; $p=0.0002$), and NT-proBNP (mean change, -21.04 ; 95% CI, -26.87 to -15.22 ; $p<0.00001$) compared with the monotherapy but did not offer any advantage in improving pulmonary vascular resistance (mean, -1.66 ; 95% CI, -3.82 to 0.5 ; $p=0.13$).

A network meta-analysis of 16 randomized controlled trials used Bayesian analysis to evaluate efficacy of agents for PAH ($n=4,112$).¹⁴⁴ The authors found that add-on therapy with either tadalafil or inhaled treprostinil compared to endothelin receptor antagonists alone improved 6MWD (27 m [95% credible interval, 11 to 43] versus 19 m [95% credible interval, 10 to 27]), respectively. In addition, add-on macitentan or bosentan improved 6MWD to a greater extent than PDE-5 inhibitors alone (26 m [95% credible interval, 6.4 to 45] and 22 m [95% credible interval, 5.1 to 38]), respectively. No significant differences were found in all-cause mortality or discontinuations due to adverse effects.

SUMMARY

The treatment for pulmonary arterial hypertension (PAH) is challenging and complicated. Untreated PAH is characterized by a progressive increase in pulmonary arterial pressure, secondary right ventricular failure, and premature death.

The American College of Chest Physicians (CHEST) 2019 guidelines for treatment of PAH in adults provides treatment recommendations based on World Health Organization (WHO) functional class (FC) for patients who are not candidates for, or who have failed, calcium channel blocker (CCB) therapy. In treatment-naïve patients with WHO FC II or WHO FC III without rapid disease progression or poor prognosis, initial combination therapy with ambrisentan and tadalafil is suggested. Monotherapy with ambrisentan, bosentan, sildenafil, macitentan, tadalafil, or riociguat is considered an alternative in patients who are unwilling to take or cannot tolerate combination therapy. For treatment-naïve patients with WHO FC IV, initial therapy with a parenteral prostanoid agent is recommended. If the patient cannot comply with parenteral administration, an inhaled prostanoid in combination with an

oral endothelin receptor antagonist (ERA) or an oral phosphodiesterase type-5 (PDE-5) inhibitor is recommended.

If symptoms still remain during treatment with an oral ERA or PDE-5 inhibitor, addition of an inhaled prostanoid is suggested. In patients with WHO FC III and continued disease progression while on oral mono- or combination therapy, addition of a parenteral or inhaled prostanoid may be considered; however, if disease progression is rapid or the patient has a poor prognosis, then a parenteral prostanoid is preferred. In patients with WHO FC III or IV and an inadequate response to initial therapy with mono- or combination therapy, a second or third class of PAH agents should be added.

While the CHEST guidelines states that the newer oral agents, selexipag (Uptravi) and treprostinil (Orenitram), may alter the therapeutic landscape of PAH treatment, they do not offer recommendations for or against their use. However, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) 2015 recommendations for the diagnosis and treatment of pulmonary hypertension include both medications as options in patients who responded to acute vasoreactivity tests. Selexipag is an option for monotherapy or in combination with an ERA and/or PDE-5 inhibitor in patients with WHO FC II or III, and oral treprostinil is recommended as an option for monotherapy in patients with WHO FC III.

Both oral PDE-5 inhibitors, sildenafil (Revatio) and tadalafil (Adcirca), improve exercise tolerance and hemodynamic status, as well as delay clinical worsening.

The oral endothelin receptor antagonists (ERAs), bosentan (Tracleer) and ambrisentan (Letairis), have been shown to improve exercise ability, hemodynamics, quality of life, and increase time to clinical worsening in short-term studies, while macitentan (Opsumit) in an event-driven study, has been shown to delay disease progression including death, initiation of prostanoid therapy, clinical worsening, and reduced hospitalization. Ambrisentan (Letairis) is approved in patients with WHO FC II and III symptoms, bosentan (Tracleer) is approved in patients with Class II–IV symptoms, and macitentan (Opsumit) is approved in patients with WHO FC I symptoms. Unlike bosentan and ambrisentan, no dosage adjustment is needed in hepatic impairment with macitentan. Riociguat (Adempas) offers a new addition to the pharmacopeia for PAH (WHO Group 1 pulmonary hypertension) and is the first FDA-approved therapy for chronic thromboembolic pulmonary hypertension (WHO Group 4 pulmonary hypertension) when patients are inoperable or have residual post pulmonary embolism (PE) hypertension. It has a dual mode of action, acting in synergy with endogenous nitric oxide (NO) and also directly stimulating soluble guanylate cyclase (sGC) independent of NO availability. Syncope is the most common serious adverse event. It is contraindicated with concomitant PDE-5 inhibitors due to hypotension. In patients with chronic thromboembolic pulmonary hypertension, riociguat has been shown to improve exercise and WHO FC. In patients with PAH, riociguat has been shown to improve exercise capacity, improve WHO FC, and to delay clinical worsening.

Selexipag (Uptravi) represents the first oral selective prostacyclin receptor agonist. It is also available in an intravenous formulation for patients with PAH who are temporarily unable to take oral therapy. Prostacyclin analogs also target vasodilation via the prostacyclin receptor, but must be administered via the IV, subcutaneous, or inhaled route. In its pivotal trial, selexipag (as monotherapy and a component of combination therapy) lowered the composite risk of all-cause mortality or PAH complication by a relative 40% compared to placebo, although the effect was driven by lower hospitalization rates and disease progression. A survival benefit has not been shown with selexipag.

The inhalation prostacyclin analogues, iloprost (Ventavis) are approved in FC III to IV and treprostinil (Tyvaso) for FC III. Iloprost (Ventavis) has demonstrated improved exercise capacity and improvements in clinical symptoms and events. Treprostinil (Tyvaso) has shown to improve exercise capacity in PAH and pulmonary hypertension associated with interstitial lung disease.

Drug selection is complex and depends on several factors including patient's disease status (e.g., functional severity, exercise capacity, cardiac index, right atrial pressure, N-terminal pro-brain natriuretic peptide P levels, Borg dyspnea score), route of administration, adverse events, patient preference, physician experience, and clinical judgment. Combination therapy should be considered for patients who do not improve with monotherapy.

REFERENCES

- 1 Letairis [package insert]. Foster City, CA; Gilead; August 2019.
- 2 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.
- 3 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.
- 4 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.
- 5 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.
- 6 Revatio [package insert]. New York, NY; Pfizer; February 2020.
- 7 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.
- 8 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.
- 9 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.
- 10 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.
- 11 Hoepfer MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013; 62: D42-40. DOI: 10.1016/j.jacc.2013.10.032. Available at: <https://www.sciencedirect.com/science/article/pii/S0735109713058750?via%3Dihub>. Accessed October 25, 2021.
- 12 Badesch DB, Champion HC, Sanchez MAG, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009; 54(1): S55-66. DOI: 10.1016/j.jacc.2009.04.011. Available at: <https://www.sciencedirect.com/science/article/pii/S0735109709012145?via%3Dihub>. Accessed October 25, 2021.
- 13 Oudiz RJ, Nazzareno G, Olschewski H, et al. For the ARIES Study Group. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009; 54(21): 1,971-1,981. DOI: 10.1016/j.jacc.2009.07.033. Available at: <https://www.sciencedirect.com/science/article/pii/S0735109709028423?via%3Dihub>. Accessed October 25, 2021.
- 14 Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62: D34-41. DOI: 10.1016/j.jacc.2013.10.029. Available at: <https://www.sciencedirect.com/science/article/pii/S0735109713058725?via%3Dihub>. Accessed October 25, 2021.
- 15 Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913. Available at: <https://erj.ersjournals.com/>. Accessed October 25, 2021.
- 16 Rosenzweig EB, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *European Respiratory Journal*. 2019; 53: 1801916; DOI: 10.1183/13993003.01916-2018. Available at: <https://erj.ersjournals.com/>. Accessed October 25, 2021.
- 17 Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913. Available at: <https://erj.ersjournals.com/>. Accessed October 25, 2021.
- 18 Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62: D34-41. DOI: 10.1016/j.jacc.2013.10.029. Available at: <http://www.acc.org/>. Accessed October 25, 2021.
- 19 Klinger JR, CG Elliott, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST Guideline and Expert Panel Report. *Chest*. 2019; 155(3): 565-586. DOI: 10.1016/j.chest.2018.11.030. Available at: <https://journal.chestnet.org/>. Accessed October 25, 2021.
- 20 Galiè N, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. *European Heart Journal*. 2016; 37: 67-119. DOI: 10.1093/eurheartj/ehv317. Available at: <https://www.escardio.org/>. Accessed October 25, 2021.
- 21 Galiè N, Corris PA, Frost A, et al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. *J Am Coll Cardiol*. 2013; 62 (25): D60-D72. DOI: 10.1016/j.jacc.2013.10.031. Available at: <http://www.acc.org/>. Accessed October 25, 2021.
- 22 Galie N, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *European Respiratory Journal*. 2019; 53: 1801889. DOI: 10.1183/13993003.01889-2018. Available at: <https://erj.ersjournals.com/>. Accessed October 25, 2021.
- 23 Mahmud E, Madani MM, Kim NH, et al. Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. *J Am Coll Cardiol* 2018; 71(21): D92-99. DOI: 10.1016/j.jacc.2018.04.009. Available at: <http://www.acc.org/>. Accessed October 25, 2021.
- 24 Ryu JH, Frantz RP. Pulmonary hypertension due to lung disease and/or hypoxemia (group 3 pulmonary hypertension): treatment and prognosis. Last updated September 13, 2021. UpToDate. Available at: <https://www.uptodate.com/contents/search>. Accessed October 25, 2021.
- 25 Letairis [package insert]. Foster City, CA; Gilead; August 2019.
- 26 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.
- 27 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.
- 28 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.
- 29 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.

30 Revatio [package insert]. New York, NY; Pfizer; February 2020.

31 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.

32 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.

33 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.

34 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.

35 Letairis [package insert]. Foster City, CA; Gilead; August 2019.

36 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.

37 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.

38 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.

39 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.

40 Revatio [package insert]. New York, NY; Pfizer; February 2020.

41 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.

42 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.

43 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.

44 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.

45 Letairis [package insert]. Foster City, CA; Gilead; August 2019.

46 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.

47 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.

48 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.

49 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.

50 Revatio [package insert]. New York, NY; Pfizer; February 2020.

51 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.

52 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.

53 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.

54 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.

55 REMS@FDA. Available at: <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>. Accessed October 25, 2021.

56 Letairis [package insert]. Foster City, CA; Gilead; August 2019.

57 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.

58 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.

59 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.

60 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.

61 Revatio [package insert]. New York, NY; Pfizer; February 2020.

62 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.

63 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.

64 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.

65 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.

66 Letairis [package insert]. Foster City, CA; Gilead; August 2019.

67 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.

68 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.

69 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.

70 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.

71 Revatio [package insert]. New York, NY; Pfizer; February 2020.

72 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.

73 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.

74 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.

75 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.

76 Letairis [package insert]. Foster City, CA; Gilead; August 2019.

77 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.

78 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.

79 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.

80 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.

81 Revatio [package insert]. New York, NY; Pfizer; February 2020.

82 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.

83 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.

84 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.

85 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.

86 Barst RJ, Gibbs JSR, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009; 54(1): 578-84. DOI: 10.1016/j.jacc.2009.04.017. Available at: <https://www.sciencedirect.com/science/article/pii/S0735109709012236?via%3Dihubhttp://www.acc.org/> Accessed October 25, 2021.

87 Letairis [package insert]. Foster City, CA; Gilead; August 2019.

88 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.

89 Opsumit [package insert]. South San Francisco, CA; Actelion; October 2021.

90 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.

91 Upravi [package insert]. South San Francisco, CA; Actelion; October 2021.

92 Revatio [package insert]. New York, NY; Pfizer; February 2020.

93 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.

- 94 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.
- 95 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.
- 96 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.
- 97 Gaile N, Ghofrani HA, Torbicki A, et al. Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005; 353(20): 2,148–2,157. DOI: 10.1056/NEJMoa050010.
- 98 Sastry BK, Narasimhan C, Reddy NK, et al. Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Amer Coll Cardiol*. 2004; 43(7): 1,149–1,153. DOI: 10.1016/j.jacc.2003.10.056.
- 99 Shah SJ, Thenappan T, Rich S, et al. Value of exercise treadmill testing in the risk stratification of Patients with pulmonary hypertension. *Circ Heart Fail*. 2009; 2(4): 278–286. DOI: 10.1161/CIRCHEARTFAILURE.108.807826.
- 100 Revatio [package insert]. New York, NY; Pfizer; February 2020.
- 101 Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus endothelin receptor antagonist for pulmonary hypertension (SERAPH) study. *Amer J Resp Crit Care Med*. 2005; 171: 1,292–1,297. DOI: 10.1164/rccm.200410–1411OC.
- 102 Galie N, Beghetti M, Gatzoulis M, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006; 114(1): 48–54. DOI: 10.1161/CIRCULATIONAHA.106.630715.
- 103 Galie N, Hinderliter A, Torbicki A, et al. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and doppler measures in patients with pulmonary arterial hypertension. *J Am Coll Cardiol*. 2003; 41(8): 1,380–1,386. DOI:10.1016/S0735-1097(03)00121-9.
- 104 Galie N, Rubin L, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomized controlled trial. *Lancet*. 2008; 371(9630): 2,093–2,100. DOI: 10.1016/S0140-6736(08)60919-8.
- 105 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.
- 106 Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002; 346(12): 896–903. DOI: 10.1056/NEJMoa012212.
- 107 Tracleer [package insert]. South San Francisco, CA; Actelion; January 2021.
- 108 Letairis [package insert]. Foster City, CA; Gilead; August 2019.
- 109 Galie N, Olschewski H, Oudiz R, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008; 117(23): 2,966–2,968. DOI: 10.1161/CIRCULATIONAHA.108.782979.
- 110 Oudiz RJ, Galie N, Olschewski H, et al. For the ARIES Study Group. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. *JACC*. 2009; 54(21): 1,971–1,981. DOI: 10.1016/j.jacc.2009.07.033.
- 111 Galie N, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med*. 2015; 373(9): 834–844. DOI: 10.1056/NEJMoa1413687.
- 112 McLaughlin V. Survival in patients with pulmonary arterial hypertension treated with first-line bosentan. *Eur J Clin Invest*. 2006; 36 Suppl 3:10-15.
- 113 McGoon MD, Frost AE, Oudiz RJ, et al. Ambrisentan therapy in patients with pulmonary arterial hypertension who discontinued bosentan or sitaxsentan due to liver function test abnormalities. *Chest*. 2009; 135(1): 122–129. DOI: 10.1378/chest.08–1028.
- 114 Letairis [package insert]. Foster City, CA; Gilead; August 2019.
- 115 Adcirca [package insert]. Indianapolis, IN; Eli Lilly; September 2020.
- 116 Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009; 119(22): 2,894–2,903. DOI: 10.1161/CIRCULATIONAHA.108.839274.
- 117 Barst RJ, Oudiz RJ, Beardsworth A, et al. Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. *J Heart Lung Transplant*. 2011; 30(6): 632–643. DOI: 10.1016/j.healun.2010.11.009.
- 118 Olschewski H, Simonneau G, Galie N, et al. Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002; 347(5): 322–329. DOI: 10.1056/NEJMoa020204.
- 119 Ventavis [package insert]. South San Francisco, CA; Actelion; December 2019.
- 120 McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respr Crit Care Med*. 2006; 174(11): 1,257–1,263. DOI: 10.1164/rccm.200603-358OC.
- 121 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.
- 122 Tapson VF, Torres F, Kermeeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C Study). *A Randomized Controlled Trial*. *Ches*. 2012; 142(6): 1,383–1,390.
- 123 Tapson VF, Jing ZC, Pan L, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (The FREEDOM-C2 Study). *A Randomized Controlled Trial*. *Chest*. 2013; 144(3): 952–958. DOI:10.1378/chest.12–2875.
- 124 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.
- 125 Rubin L, Parikh K, Pulido T, et al. FREEDOM-M: Efficacy and safety of oral treprostinil diethanolamine as monotherapy in patients with pulmonary arterial hypertension. *Chest*. 2011; 140: 1044A DOI:10.1378/chest.1212098.
- 126 Orenitram [package insert]. Research Triangle Park, NC; United; May 2021.
- 127 White RJ, Jerjes-Sanchez C, Bohns Meyer GM, et al. Combination Therapy with Oral Treprostinil for Pulmonary Arterial Hypertension: A Double-Blind, Placebo-Controlled Study. *Am J Respr Crit Care Med*. 2019; 201(6): 707–717. DOI: 10.1164/rccm.201908-1640OC.
- 128 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.
- 129 McLaughlin V, Rubin L, Benza R, et al. TRIUMPH I: efficacy and safety of inhaled treprostinil sodium in patients with pulmonary arterial hypertension (PAH). *Am J Respr Crit Care Med*. 2008; 177: A965. DOI: 10.1517/13543784.17.6.965.
- 130 McLaughlin V, Benza R, Rubin L, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010; 55(18): 1,915–1,922. DOI: 10.1016/j.jacc.2010.01.027.
- 131 Tyvaso [package insert]. Research Triangle Park, NC; United; March 2021.
- 132 Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med*. 2021;384(4): 325–334. DOI: 10.1056/NEJMoa2008470.

-
- 133 Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369(9): 809–818. DOI: 10.1056/NEJMoa1213917.
- 134 Ghofrani HA, D'Armini AM, Grimminger F, et al. for the CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013; 369: 319-329. DOI: 10.1056/NEJMoa1209657.
- 135 Adempas [package insert]. Whippany, NJ; Bayer; September 2021.
- 136 Ghofrani HA, Galiè N, Grimminger F, et al. for the PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 330-340. DOI: 10.1056/NEJMoa1209655.
- 137 Hoepfer MM, Al-Hiti H, et al. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med*. 2021; 9(6): 573-584. DOI: 10.1016/S2213-2600(20)30532-4. Available at: [https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30532-4/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30532-4/fulltext). Accessed October 25, 2021.
- 138 Sitbon O, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med* 2015; 373: 2,522-2,533. DOI: 10.1056/NEJMoa1503184.
- 139 Galie N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J*. 2009; 30: 394-403. DOI: 10.1093/eurheartj/ehp022.
- 140 Ryerson CJ, Nayar S, Swiston JR, et al. Pharmacotherapy in pulmonary arterial hypertension: a systematic review and meta-analysis. *Respir Res*. 2010; 11:12. DOI: 10.1186/1465-9921-11-12.
- 141 Macchia A, Marchioli R, Tognoni G, et al. Systematic review of trials using vasodilators in pulmonary arterial hypertension: when a new approach is needed. *Am Heart J*. 2010; 159(2): 245-257. DOI: 10.1016/j.ahj.2009.11.028.
- 142 Barnes H, Brown Z, Burns A, et al. Phosphodiesterase 5 inhibitors for pulmonary hypertension. *Cochrane Database Syst Rev*. 2019; 1: CD012621. DOI: 10.1002/14651858.CD012621.pub2.
- 143 Kirtania L, Maiti R, Srinivasan A, et al. Effect of combination therapy of endothelin receptor antagonist and phosphodiesterase-5 inhibitor on clinical outcome and pulmonary haemodynamics in patients with pulmonary arterial hypertension: A meta-analysis. *Clin Drug Investig*. 2019; 39(11): 1,031-1,044 DOI: 10.1007/s40261-019-00841-1.
- 144 Petrovic M, Locatelli I. A Bayesian network meta-analysis of add-on drug therapies specific for pulmonary arterial hypertension. *Ann Pharmacother*. 2020; 54(5): 423-433. DOI: 10.1177/1060028019888760.