



Pulmonary Arterial Hypertension (PAH) Agents, Oral and Inhaled

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Oral Agents		
ambrisentan (Letairis™) ¹	Gilead Sciences	Treatment of pulmonary arterial hypertension (World Health Organization [WHO] Group I) to improve exercise ability and delay clinical worsening.
bosentan (Tracleer®) ²	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II to IV symptoms, to improve exercise ability and decrease clinical worsening.
macitentan (Opsumit®) ³	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) to delay disease progression which includes death, initiation of intravenous (IV) or subcutaneous (SC) prostanoids, or clinical worsening. Opsumit also reduced 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. Pulmonary arterial hypertension (WHO Group I) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.
sildenafil (Revatio™) ⁵	generic Pfizer	Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening.
tadalafil (Adcirca™) ⁶	Eli Lilly	Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability.
treprostinil (Orenitram™) ⁷	United Therapeutics	Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise capacity.
Inhalation Agents		
iloprost (Ventavis®) ⁸	Actelion	Treatment of pulmonary arterial hypertension (WHO Group I) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.
treprostinil (Tyvaso™) ⁹	United Therapeutics	Treatment of pulmonary arterial hypertension (WHO Group I) to increase 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 ambrisentan (Letairis) and oral treprostinil (Orenitram) effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (64 and 75 percent, respectively) or PAH associated with connective tissue diseases (32 and 19 percent, respectively). Studies establishing bosentan (Tracleer) effectiveness included predominately patients with NYHA Functional Class II–IV symptoms and etiologies of idiopathic or heritable PAH (60 percent), PAH associated with connective tissue diseases (21 percent), and PAH associated with congenital systemic-to-pulmonary shunts (18 percent). Studies establishing macitentan (Opsumit) effectiveness included predominately patients with WHO Functional Class II–IV symptoms and etiologies of idiopathic or heritable PAH (57 percent), PAH associated with connective tissue disorders (31 percent), and PAH associated with congenital heart disease with repaired shunts (eight percent). Studies establishing riociguat (Adempas) effectiveness included predominately patients with WHO Functional Class II–III symptoms and etiologies of idiopathic (61 percent) or familial PAH (two percent), PAH associated with connective tissue disease (25 percent), and PAH associated with congenital heart disease (eight

percent). Studies establishing sildenafil (Revatio) effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of primary pulmonary hypertension (71 percent) or pulmonary hypertension associated with connective tissue disease (25 percent). Studies establishing tadalafil (Adcirca) effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61 percent) or PAH associated with connective tissue diseases (23 percent). Studies establishing iloprost (Ventavis) effectiveness included predominately patients with NYHA Functional Class III–IV symptoms and etiologies of idiopathic or heritable PAH (65 percent) or PAH associated with connective tissue diseases (23 percent). Studies establishing inhaled treprostinil (Tyvaso) effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56 percent) or PAH associated with connective tissue diseases (33 percent).

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 as a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg.¹⁰ Criterion of mPAP with exercise > 30 mm Hg has been removed due to the lack of a suitable definition regarding level, type, and posture. 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.¹¹ 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 percent mortality within the first five years after diagnosis.¹² Management of PH should be limited to specialized centers where clinicians are experienced in the evaluation and treatment of patients with PH.¹³

The WHO classifies PH patients into five groups based on etiology. Group I now refers to pulmonary arterial hypertension (PAH); the other four groups describe PH.¹⁴ Each group has subgroups. Collectively all five 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.¹⁵

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 (BMPR2) gene plays a key role in the pathogenesis of heritable PAH.¹⁶ Other etiologies in PAH include drugs and toxins, collagen vascular resistance, 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 (FC).¹⁷ 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.

In December 2013, an American College of Cardiology updated treatment algorithm for PAH was published in the Journal of American College of Cardiology (JACC) and discusses the Fifth World Symposium on Pulmonary Hypertension which took place in Nice, France, in 2013.¹⁸ It should be noted that different treatments have been evaluated mainly in idiopathic PAH, heritable PAH, in PAH associated with the connective tissue diseases or with congenital heart disease and anorexigen use. Therefore, caution is warranted when extrapolating these recommendations to other PAH subgroups, particularly those with PH associated with left heart disease (Group 2) or with lung diseases (Group 3).

The following is a summary of the evidence-based PAH treatment algorithm published in the JACC.

- At the time of diagnosis of PAH, in addition to general measures (exercise training, rehabilitation), oral anticoagulation, diuretics, and digoxin are recommended (expert opinion), but data on long-term effects are lacking. Long-term oxygen therapy is suggested to maintain arterial blood O₂ pressure ≥ 8 kPa (60 mm Hg).
- A trial of high dose oral calcium channel blockers (CCB) (Grade B), such as dihydropyridine type or diltiazem, is recommended only in a minority of patients with IPAH with a positive acute vasoreactive test. These patients should be followed closely for both safety and efficacy of this therapy. Patients with PAH due to conditions other than IPAH have a very low rate of long-term responsiveness to oral CCBs. Inhaled nitric oxide (iNO) is the compound of choice for the acute test and, on the basis of previous experience, intravenous epoprostenol or adenosine may also be used as an alternative (but with a risk of systemic vasodilator effects). Inhaled iloprost has also been used to identify patients who may benefit from long-term therapy with CCBs.¹⁹
- Nonresponders to acute vasoreactivity testing who are WHO functional class (WHO-FC) II should be treated with an oral agent.
- Patients with a negative response to the acute vasoreactivity test with any functional class, or positive responders who remain in WHO-FC III, are considered candidates for treatment with any PAH-approved drugs: prostacyclins, endothelin receptor antagonists (ERAs), an oral soluble guanylate cyclase stimulator, or a phosphodiesterase-5 inhibitor (PDE-5 inhibitors). Specific recommendations:
 - ❑ WHO-FC II: ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), riociguat (Adempas), sildenafil (Revatio), and tadalafil (Adcirca) (Level I, Grade A or B for all). Macitentan has shown reduction in the composite endpoint of morbidity and mortality among patients with PAH.
 - ❑ WHO-FC III: ambrisentan, bosentan, intravenous epoprostenol, inhaled iloprost (Ventavis), macitentan, riociguat, sildenafil, tadalafil, subcutaneous or inhaled treprostinil (Remodulin®, Tyvaso) (Level I, Grade A or B for all); intravenous iloprost (Ventavis), intravenous treprostinil (Remodulin) (Level IIa, Grade C).

- WHO-FC IV: Continuous intravenous epoprostenol (Flolan®) (Level I, Grade A) – improves exercise capacity, hemodynamics, and survival in FC IV. This is the treatment of choice for the most critically ill patients. Epoprostenol is also the only therapy for PAH that has been shown to prolong survival²⁰; ambrisentan, bosentan, intravenous/inhaled iloprost, macitentan, riociguat, sildenafil, tadalafil, intravenous/subcutaneous/inhaled treprostinil are alternatives (Level IIa, Grade C). In WHO-FC IV patients, initial combination therapy may also be considered (Level IIb, Grade C).
- Combination therapy with two agents with different mechanisms of action is recommended in patients with inadequate response to PAH monotherapy. The optimal combination on the basis of overall risk-benefit remains unknown, but could include sequential combination therapy with: ERAs plus prostanoids; ERAs plus PDE-5 inhibitors or soluble guanylate cyclase stimulator; or prostanoids plus PDE-5 inhibitors or soluble guanylate cyclase stimulator. In case of inadequate clinical response with double combination therapy, triple combination therapy should be attempted. The combination of riociguat and PDE-5 inhibitors is contraindicated.
- Atrial septostomy and lung transplantation are indicated for refractory patients or where medical treatment is unavailable.
- Oral treprostinil (Orenitram) was not FDA approved at the time of publication of this treatment algorithm and is FDA approved to treat patients with WHO FC II-III symptoms.

The Food and Drug Administration (FDA) approved treatments for PAH include prostacyclin and prostacyclin analogs [intravenous epoprostenol (Flolan), intravenous room stable epoprostenol (Veletri), treprostinil (oral Orenitram/intravenous, SC Remodulin/inhalation Tyvaso), iloprost (Ventavis)], 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 (Letairis), bosentan (Tracleer), macitentan (Opsumit), riociguat (Adempas), treprostinil (Orenitram), sildenafil (Revatio), and tadalafil (Adcirca)] and inhaled medications [iloprost (Ventavis) and treprostinil (Tyvaso)] for the treatment of pulmonary arterial hypertension (PAH).

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable cause of PH.²¹ Radionuclide ventilation/perfusion (VQ) scan is the preferred and recommended screening test for chronic thromboembolic disease in patients with PH. 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 is the only FDA approved agent for CTEPH in this review.

PHARMACOLOGY^{22, 23, 24, 25, 26, 27, 28, 29}

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.

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

Drug	Half-life (hours)	Bioavailability (%)	Metabolite	Excretion (%)
Oral Agents				
ambrisentan (Letairis) ³⁰	9	Unknown	Unknown	Renal: minor Non-Renal: major
bosentan (Tracleer) ³¹	5	50	Two inactive and one active that contributes 10–20 percent of parent drug activity	Renal: 3 Feces: 97
macitentan (Opsumit) ³²	16 (parent drug) 48 (active metabolite)	Unknown	One active metabolite that contributes approximately 40 percent of the total pharmacological activity	Renal: 50 Feces: 24
riociguat (Adempas) ³³	12	94	Major metabolite is M1 and is 1/3 to 1/30 as potent as riociguat	Renal: 40 Feces: 53
sildenafil (Revatio) ³⁴	4 (for parent drug and metabolite)	41	N-desmethyl metabolite (active with <i>in vitro</i> potency of PDE-5–50 percent of parent drug)	Renal: 13 Feces: 80
tadalafil (Adcirca) ³⁵	*15	Unknown	Major metabolite is methylcatechol glucuronide which is considered inactive	Feces: 61 Renal: 36
treprostinil (Orenitram) ³⁶	4	17	Five inactive metabolites (four are products of oxidation of the 3-hydroxyloctyl side chain; one is a glucuronide conjugated derivative: treprostinil glucuronide)	Feces: 13 Renal: 79
Inhalation Agents				
iloprost (Ventavis) ³⁷	20 to 30 minutes	Unknown	Main metabolite is tetranor-iloprost (inactive in animal studies)	Feces: 12 Renal: 68
treprostinil (Tyvaso) ³⁸	4	64 to 72 (dose dependent)	Five inactive metabolites (four are products of oxidation of the 3-hydroxyloctyl side chain and one 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^{39,40,41,42,43,44, 45,46,47}

Ambrisentan (Letairis) is contraindicated in pregnancy and has a black box warning regarding the likelihood of serious birth defects if used by pregnant women. Females of reproductive potential must use acceptable methods of contraception and obtain monthly pregnancy tests while being treated with ambrisentan and for one month following discontinuation of the medication. Due to the risk of embryo-fetal toxicity, ambrisentan is available only through a special restricted distribution program for pharmacies, prescribers, and patients known as LEAP (Letairis Education and Access Program) by calling 1-866-664-5327.

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 five times ULN or if elevations are accompanied by bilirubin greater than two times ULN, or by signs or symptoms of liver impairment and other causes are excluded.

Bosentan (Tracleer) has two black box warnings related to potentially serious liver injury and teratogenicity. Bosentan has caused at least three times the ULN elevation of liver aminotransferases (ALT and AST) in about 11 percent of patients, accompanied by elevated bilirubin in a small number of cases, warranting serum aminotransferase monitoring. 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 x ULN). Strict adherence to the monthly monitoring schedule for the duration of treatment is required to use bosentan. Bosentan is likely to cause major birth defects if used by pregnant females; therefore, it is considered a teratogenic substance. Due to the significant potential for fetal harm, as well as the potential for serious liver damage, bosentan can only be accessed through the Tracleer Access Program (TAP) by calling 1-866-228-3546. Concomitant use of bosentan with cyclosporine A or with glyburide is contraindicated due to increased bosentan levels and increased liver enzymes, respectively.

If signs of pulmonary edema occur in patients on ambrisentan, bosentan, macitentan (Opsumit), 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.

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.

Macitentan and riociguat are contraindicated in pregnancy and carry a black box warning for embryo-fetal toxicity. These medications must not be administered to pregnant females due to fetal harm. 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. For female patients, macitentan is only available through the Opsumit REMS program and riociguat is only available through the Adempas REMS program.

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) due to an increased risk for hypotension.

Concurrent administration of organic nitrates (nitroglycerin) in any form with sildenafil (Revatio) or tadalafil (Adcirca) is contraindicated as the combination potentiates the hypotensive effects.

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.

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

Phosphodiesterase type 5 (PDE-5) inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing tadalafil, physicians should carefully consider whether their patients with underlying cardiovascular disease 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 Adcirca to these patients is not recommended. The use of tadalafil with alpha blockers, blood pressure medications, and alcohol may also lower blood pressure significantly and may lead to symptomatic hypotension (fainting). Inhaled iloprost (Ventavis) and treprostinil (Tyvaso) have not been evaluated in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease) or with acute pulmonary infections. Such patients should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Both agents can cause symptomatic hypotension in patients with low systemic arterial pressure. Both agents inhibit platelet aggregation, so there may be an increased risk of bleeding, particularly among patients receiving anticoagulation.

Should 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 (Ventavis) 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 chronic obstructive pulmonary disease (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.

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 inhibits platelet aggregation and leads to an increased risk of bleeding.

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.

Risk Evaluation and Mitigation Strategy (REMS)^{48,49,50,51}

Ambrisentan (Letairis) and bosentan (Tracleer) have a REMS program which includes a Medication Guide, elements to ensure safe use, and implementation systems.

Macitentan (Opsumit) and riociguat (Adempas) require all female patients enroll in their respective REMS program. Based on the reproductive potential of the patient, the programs include a medication guide, monthly pregnancy testing, patient counseling for pregnancy planning, and a requirement for contraception.

DRUG INTERACTIONS^{52,53,54,55,56,57,58,59,60}

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 two-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 two 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.

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.

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

Drug	Epistaxis	Head-ache	Dyspepsia	Flushing	Insomnia	Erythema	Elevations in ALT/AST (> 3X ULN)
Oral Agents							
ambrisentan (Letairis) ⁶¹	nr	15 (14)	nr	4 (1)	nr	nr	0
bosentan (Tracleer) ⁶²	nr	22 (20)	4 (0)	9 (5)	nr	nr	11 (2)
macitentan (Opsumit) ⁶³	nr	14 (9)	nr	nr	nr	nr	3.4 (4.5)
riociguat (Adempas) ⁶⁴	nr	27 (18)	21 (8)	nr	nr	nr	nr
sildenafil 20 mg three times daily (Revatio) ⁶⁵ n=69 (placebo n=70)	9 (1)	46 (39)	13 (7)	10 (4)	7 (1)	6 (1)	nr
tadalafil 40 mg/day (Adcirca) ⁶⁶ n=79 (placebo n=82)	nr	42 (15)	10 (2)	13 (2)	nr	nr	nr
treprostinil (Orenitram) ⁶⁷	nr	63 (19)	nr	15 (6)	nr	nr	nr
Inhalation Agents							
iloprost (Ventavis) ⁶⁸ n=101 (placebo n=102)	39 (26)	27 (9)	30 (20)	12 (3)	13 (8)	8 (5)	nr
treprostinil (Tyvaso) ⁶⁹ 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.

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. An observational study suggests an approximate two fold increase in the risk of NAION within one to four 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.^{70,71} As with other PDE-5 inhibitors, there have been rare reports of priapism related to sildenafil and tadalafil therapy.^{72,73}

Reduced sperm counts, which may impair a man's ability to father children, have been observed in patients taking endothelin receptor antagonists (ERAs).^{74,75,76}

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.⁷⁷

Common adverse events reported with use of oral treprostinil (Orenitram) and more frequently than placebo include diarrhea (30 versus 16 percent), nausea (30 versus 18 percent), pain in extremity (14 versus eight percent), and jaw pain (11 versus four percent).⁷⁸ The most common adverse events reported with inhaled treprostinil and more frequently than placebo (Tyvaso) are cough (54 versus 29 percent) and throat irritation (41 versus 23 percent). 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.⁷⁹

SPECIAL POPULATIONS^{80,81,82,83,84,85,86,87,88}

Pediatrics

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

Pregnancy

Ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), and riociguat (Adempas) are categorized as Pregnancy Category X and are expected to cause fetal harm if administered to pregnant women. Pregnancy must be excluded before initiating therapy with these products and prevented thereafter using reliable methods of birth control.

Sildenafil (Revatio) and tadalafil (Adcirca) are categorized as Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women.

Iloprost (Ventavis) and treprostinil (Orenitram, Tyvaso) are categorized as Pregnancy Category C and B, respectively.

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) in patients with creatinine clearance greater than or equal to 15 mL/min. Safety and efficacy has not been established in patients with creatinine clearance less than 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 (51–80 mL/min) to moderate impairment (31–50 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 five 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 Black Box 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 x upper limit of normal (ULN) is about 11 percent with bosentan and zero percent with ambrisentan.^{89,90} 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 has 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 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 – 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., three to four 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 is contraindicated in those with severe impairment.

Geriatric Patients

In the clinical studies of tadalafil (Adcirca) for pulmonary arterial hypertension, 28 percent were 65 years of age and over, while 8 percent 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 two placebo-controlled clinical studies of ambrisentan (Letairis), 21 percent of patients were ≥ 65 years old and five percent 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 percent 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 in riociguat (Adempas), 23 percent were ≥ 65 years and six percent 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.

Clinical studies of bosentan (Tracleer), sildenafil (Revatio), iloprost (Ventavis), and treprostinil (Orenitram, Tyvaso) did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. 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.

DOSAGES

Drug	Initial Dose	Maximum Daily Dose	How Supplied
Oral Agents			
ambrisentan (Letairis) ⁹¹	5 mg once daily with or without food	10 mg once daily	5, 10 mg tablets
bosentan (Tracleer) ⁹²	62.5 mg twice daily for first four weeks	125 mg twice daily	62.5, 125 mg tablets
macitentan (Opsumit) ⁹³	10mg once daily with or without food	10mg once daily	10 mg tablets
riociguat (Adempas) ⁹⁴	1 mg three times a day with or without food	2.5 mg three times a day	0.5, 1, 1.5, 2, 2.5 mg tablets
sildenafil (Revatio) ⁹⁵	Oral: 5 mg or 20 mg three times, 4-6 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 (12.5 mL) single-use vial 10mg/mL oral suspension
tadalafil (Adcirca) ⁹⁶	40 mg once daily with or without food	40 mg once daily with or without food	20 mg tablet
treprostinil (Orenitram) ⁹⁷	0.25 mg twice daily with food	Determined by tolerability	0.125 mg, 0.25 mg, 1 mg, 2.5 mg extended-release tablets
Inhalation Agents			
iloprost (Ventavis) ⁹⁸	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) ⁹⁹	18 mcg (3 inhalations) four times daily about 4 hours apart; if 3 inhalations not tolerated reduce to 1-2 inhalations as tolerated	54 mcg (or 9 inhalations) four times daily.	2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL) oral inhalation solution

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.

Riociguat (Adempas) treatment should be initiated at 1 mg taken three 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 two 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 three or more days.

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.

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 three to four days, as tolerated, until desired clinical response is achieved.¹⁰⁰ 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. Avoid abrupt discontinuation or sudden large reductions in dose. If a dose is missed, take the missed dose as soon as possible. If two or more doses are missed, restart at a lower dose and re-titrate.

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 four treatment sessions in a single day. The effects diminish over the minimum recommended dosing interval of four hours; therefore, treatment timing can be adjusted for planned activities.

Iloprost (Ventavis) is intended to be inhaled using either of two 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 two hours and that the acute benefits may not last two 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, 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 percent 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) and placebo

In a randomized, double-blind, placebo-controlled study, 278 patients (277 randomized, one patient not treated) with symptomatic PAH received placebo or sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks.¹⁰¹ The primary endpoint of distance walked in six minutes that increased 45 m (+13 percent), 46 m (+13.3 percent), and 50 m (+14.7 percent) 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, World Health Organization (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 six minutes at one 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.¹⁰² The primary endpoint was the change in exercise time on treadmill using the Naughton protocol (a graded exercise evaluation treadmill stress test).¹⁰³ Exercise time increased by 44 percent 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 functional class 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.¹⁰⁴ The primary endpoint showed that there was a statistically significant greater increase in six-minute walk distance 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 four m for the placebo group, giving an adjusted treatment difference of 26 m (95 percent CI, 10.8 to 41.2, $p=0.0009$). Patients in the placebo group were three 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) and bosentan (Tracleer)

In a double-blind trial, 26 patients with PAH (WHO functional class III) were randomized to receive sildenafil 50 mg twice daily for four weeks then 50 mg three times daily or bosentan 62.5 mg twice daily for four weeks then 125 mg twice daily over 16 weeks. Intention-to-treat analysis showed no significant differences between the two treatment groups as both improved right ventricular (RV)

mass, six-minute walk distance, and cardiac index.¹⁰⁵ Study doses of sildenafil exceeded FDA labeled doses.

bosentan (Tracleer) and 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 functional class III Eisenmenger syndrome. Hemodynamics was assessed by right- and left-heart catheterization.¹⁰⁶ 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 six-minute walk distance, 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 one percent (95 percent 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, two (five percent) in the bosentan group and two (12 percent) 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.¹⁰⁷ Patients had primary pulmonary hypertension (84 percent) 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 six-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).^{108,109} The primary endpoints were pulmonary vascular resistance (PVR) at month six (expressed as a percentage of baseline) and change from baseline in six-minute walk distance.

Compared with placebo, bosentan treatment was associated with a reduced incidence of worsening of at least one functional class (three percent for bosentan versus 13 percent for placebo, p=0.03) and improvement in hemodynamic variables (including PVR, p<0.05). The +19 m mean (+14 m median) increase in six-minute walk distance 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 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 eight 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 four weeks, followed by either of two doses of bosentan (125 or 250 mg) twice daily for a minimum of 12 weeks.¹¹⁰ At week 16, patients treated with bosentan had an improved six-minute walking distance (primary endpoint); the mean difference between the placebo group and the combined bosentan groups was 44 m (95 percent 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.

ambrisentan (Letairis) and 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).^{111,112} 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 six-minute walk distance. Both studies showed that active treatment with ambrisentan resulted in significant improvement in six-minute walk distance 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 two of the following: a 20 percent decrease in the six-minute walk distance; 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 percent; $p = 0.03$ and ARIES-2: 94 versus 79 percent; $p = 0.005$).

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.¹¹³ After two years, mean change from baseline in six-minute walk distance was improved for the 5 mg (+23 m; 95% CI, 9 to 38 m) and 10 mg (+28 m; 95 percent CI, 11 to 45 m) groups. Estimates of survival and freedom from clinical worsening for the combined dose group were 94 percent and 83 percent, respectively, at one year and 88 percent and 72 percent, respectively, at two years. Ambrisentan was generally well tolerated.

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 two double-blind, randomized trials and their open-label extensions, treated with first-line bosentan, with a three year follow-up.¹¹⁴ 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.^{115,116}

tadalafil (Adcirca) and 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.^{117,118} Of the patients in the study, 53 percent 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 six minutes. Secondary endpoints included: changes in World Health Organization (WHO) functional class, clinical worsening, and health-related quality of life. Tadalafil was found to increase the distance walked in six 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 percent CI, 15 to 50 m). The treatment effect was greater in the bosentan-naïve group, with an increase of 44 m (95 percent CI, 20 to 69 m) compared with 23 m (95 percent 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 percent 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.¹¹⁹ Patients randomized to tadalafil or placebo ($n = 405$) were analyzed by bosentan use (yes=216, no=189). Treatment differences in 6-minute walk distance (placebo-adjusted 6MWD), functional class, clinical worsening, and adverse events were assessed. At week 16, placebo-adjusted 6MWD increases were 44 m (95 percent CI: 20 to 69 m; $n = 37$) for tadalafil 40 mg in treatment-naïve patients and 23 m (95 percent CI: -two 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 three m and increased by 19 m, respectively. Five percent of treatment-naïve patients had clinical worsening with tadalafil 40 mg compared with 22 percent with the placebo group (HR= 3.3, 95 percent CI: 1.1 to ten). Five percent on background bosentan patients had clinical worsening with tadalafil 40 mg add-on compared with 11 percent for placebo add-on (HR=1.9, 95 percent 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) and 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, six to nine times per day) or placebo for 12 weeks.^{120,121} The primary endpoint was improvement of WHO class and greater than 10 percent improvement in six-minute walk test and was greater in the iloprost group versus placebo (17 versus five percent, $p=0.0007$).

iloprost (Ventavis) and bosentan

In a randomized, multicenter, double-blind trial, inhaled iloprost (5 mcg) or placebo was added to stable monotherapy with bosentan for 12 weeks.¹²² Efficacy endpoints included change from baseline in six-minute walk distance (six-MWD), modified New York Heart Association (NYHA) functional class, hemodynamic parameters, and time to clinical worsening. A total of 67 patients with PAH (55 percent IPAH, 45 percent associated PAH, 94 percent NYHA class III, and mean baseline six-MWD of 335 m) were randomized. At Week 12, patients receiving iloprost had a mean increase in six-MWD of 30 m ($p=0.001$); placebo patients had a mean six-MWD increase of four m ($p=0.69$), with a placebo-adjusted difference of +26 m ($p=0.051$). NYHA status improved by one class in 34 percent of iloprost versus six percent 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) and placebo

FREEDOM-C/C2.^{123,124,125} 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 percent) and FC III (77 percent) 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.^{126,127} 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 percent) and FC III (66 percent) 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 six-minute walk distance (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 percent 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 ($n=824$).¹²⁸

treprostinil inhalation (Tyvaso) and 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 three months prior to study initiation.^{129,130,131} 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 four daily treatment sessions with a target dose of nine breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82 percent); bosentan was the concomitant oral medication in 70 percent of those enrolled; sildenafil in 30 percent. Patients taking treprostinil in four daily inhalation sessions achieved a 20-meter improvement in six-minute walk distance over those taking placebo ($p<0.0005$). The safety and effectiveness in patients with underlying lung disease has not been established.

macitentan (Opsumit) and placebo

SERPAHIN:¹³² The effect of macitentan on progression of PAH was demonstrated in a placebo-controlled, multicenter, event-driven, trial in patients with symptomatic (WHO functional class 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 three of the following occurring: a sustained ≥ 15 percent decrease from baseline in six minute walk distance (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 percent) were being treated with a stable dose of specific therapy for PAH, either oral phosphodiesterase inhibitors (61 percent) and/or inhaled/oral prostanoids (six percent).

A total of 287 patients had a primary endpoint over a median treatment period of 115 weeks: 116 (46.4 percent) in the placebo group, 95 patients (38 percent) in the 3 mg group, and 76 patients (31.4 percent) in the 10 mg group. Treatment with macitentan 10 mg resulted in a 45 percent reduction (Hazard Ratio 0.55, 97.5 percent Confidence Interval 0.39–0.76; 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 percent in patients receiving macitentan 10 mg compared to placebo (HR 0.50, 97.5 percent CI 0.34–0.75; 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 percent), 34 (13.6 percent), and 26 (10.7 percent), 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 percent of patients receiving macitentan 10 mg.

riociguat (Adempas) and placebo

Chronic ThromboEmbolic Pulmonary Hypertension sGC-Stimulator Trial (CHEST-1):¹³³ 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 the distance walked in 6 minutes (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 percent of patients had inoperable CTEPH, 28 percent had recurrent or persisting pulmonary hypertension following pulmonary endarterectomy. At baseline, the majority of patients had a WHO functional class II (31 percent) or III (64 percent). 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 percent confidence interval [CI], 25 to 67; $p < 0.001$). Patients receiving riociguat (83 percent) experienced an improvement in 6MWD compared to 57 percent 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 percent 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 three 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 three percent of patients in each group and syncope in two percent for riociguat versus three percent for placebo. CHEST-2 was an open-label extension study of the CHEST-1 trial.

riociguat (Adempas) versus placebo

Pulmonary Arterial Hypertension sGC-Stimulator Trial (PATENT-1):¹³⁴ 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 three months or more were eligible. A total of 50 percent of the patients were treatment-naïve with respect to PAH therapy, 44 percent were pre-treated with an ERA and six percent 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), N-terminal pro-brain natriuretic peptide (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 percent confidence interval [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 percent CI) and in those who were receiving ERAs or prostanoids (least-squares mean difference, 34 m; 95 percent 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 four 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 (one versus four percent, respectively). PATENT-2 was an open-label long-term extension study of PATENT-1.

META-ANALYSIS

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 percent, RR 0.57, 95 percent CI, 0.35-0.92).¹³⁵ The average duration of the trials was 14.3 weeks.

A systematic review and meta-analysis through November 2009 included 3,758 patients.¹³⁶ Data was pooled for three classes of medications: prostanoids, endothelin-receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors. Pooled relative risks (RRs) and 95% confidence intervals were calculated for mortality, six-minute walk distance, dyspnea scores, hemodynamic parameters, and adverse effects. Mortality in the control arms was a combined 4.2 percent over the mean study length of 14.9 weeks. There was significant mortality benefit with prostanoid treatment (RR 0.49, 95 percent CI, 0.29 to 0.82), particularly comparing intravenous agents to control (RR 0.30, 95 percent CI, 0.14 to 0.63). Mortality benefit was not observed for ERAs (RR 0.58, 95% CI, 0.21 to 1.60) or PDE5 inhibitors (RR 0.30, 95 percent CI, 0.08 to 1.08). All three 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 PDE5 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 percent (95 percent CI, 2–62 percent, $p = 0.041$).¹³⁷ 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 six-minute walk distance, or hemodynamics.

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.

According to the Fifth World Symposium updated treatment algorithm for PH, nonresponders to acute vasoreactivity testing or responders who remain in WHO FC III PAH are candidates for treatment with any of the approved PAH drugs: an ERA, a PDE-5 inhibitor, an oral soluble guanylate cyclase stimulator, or a prostanoid. Among prostanoids, iloprost (Ventavis) and treprostinil (Tyvaso) can be administered by oral inhalation. Oral treprostinil (Orenitram) was not FDA approved at the time of publication of this treatment algorithm. It is FDA approved to treat patients with WHO FC II-III symptoms.

Recommendations for treatment of WHO FC II include the oral agents ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), riociguat (Adempas), sildenafil (Revatio), and tadalafil (Adcirca) (Grade A or B for all).

Recommendations for WHO FC III include the oral agents ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio), and tadalafil (Adcirca), (Grade A for all except B for tadalafil), as well as inhaled iloprost (Ventavis), inhaled and subcutaneous treprostinil (Tyvaso, Remodulin).

Since head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be recommended for patients with WHO FC II or III. In WHO FC III, initial combination therapy, and in case of inadequate clinical response, sequential combination therapy, with double or triple regimens, can be considered. Continuous intravenous epoprostenol, a synthetic prostacyclin, remains first-line for PAH FC IV due to its demonstrated survival benefit. In the absence of intravenous epoprostenol, all other compounds may be utilized. Ambrisentan, bosentan, intravenous/inhaled iloprost, macitentan, riociguat, sildenafil, tadalafil, and intravenous/subcutaneous treprostinil are considered alternatives (Grade C). Although ambrisentan, bosentan, and sildenafil are FDA-approved in WHO FC IV patients, only a small number of these patients were included in the studies. Therefore, these treatments are considered second-line in severely ill patients. In WHO FC IV patients, initial combination therapy may also be considered.

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 Functional Class 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 CTEPH (WHO Group 4 pulmonary hypertension) when patients are inoperable or have residual post PEA hypertension. It has a dual mode of action, acting in synergy with endogenous NO and also directly stimulating 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 CTEPH, riociguat has been shown to improve exercise and WHO functional class. In patients with PAH, riociguat has been shown to improve exercise capacity, improve WHO functional class, and to delay clinical worsening.

The inhalation prostacyclin analogues, iloprost (Ventavis) are approved in FC III to IV and treprostinil (Tyvaso) for FC III. Iloprost (Ventavis) has improved exercise capacity and improvements in clinical symptoms and events. Treprostinil (Tyvaso) has shown to improve exercise capacity.

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, NT-proBNP 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.

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