Pulmonary Hypertension

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO145

Description

Ambrisentan (generic, Letairis®), bosentan (generic, Tracleer®), and macitentan (Opsumit®) are endothelin receptor agonists (ERA) that inhibit the binding of endothelin – a vasoconstrictive peptide – to its receptors (ET_A and ET_B) in the endothelium and smooth muscle cells which results in vasodilation.

Tadalafil/macitentan (Opsnvi) is a combination product consisting of a phosphodiesterase type 5 (PDE5) inhibitor and an endothelin receptor agonist (ERA).

Riociguat (Adempas®) stimulates soluble guanylate cyclase (sGC) – a receptor for nitric oxide and an enzyme in the cardiopulmonary system. It sensitizes sGC to endogenous nitric oxide by stabilizing nitric oxide-sGC binding and directly stimulating sGC via a different binding site. Stimulating the nitric oxide-sGC-cGMP pathway, leads to an increased generation of cGMP and subsequent vasodilation.

Iloprost (Ventavis®) inhalation solution, treprostinil (Tyvaso®) inhalation solution, treprostinil (Orenitram®) tablets for oral use, treprostinil (Remodulin®) injection for subcutaneous use and selexipag (Uptravi®) tablets for oral use are prostacyclin vasodilators. They directly vasodilate pulmonary and systemic arterial vascular beds, inhibit platelet aggregation, and inhibit smooth muscle cell proliferation.

Sotatercept (Winreviar) is an activin signaling inhibitor that binds to Activin A and other TGF-β superfamily ligands, which improves the balance between the pro-proliferative and anti-proliferative signaling to modulate vascular proliferation.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ambrisentan (Letairis)	Pulmonary arterial hypertension (PAH)	5 mg tablets	30 tablets/30 days
		10 mg tablets	
generic ambrisentan		5 mg tablets	30 tablets/30 days
		10 mg tablets	
bosentan (Tracleer)		32 mg tablet for oral suspension	120 tablets/30 days

		62.5 mg film-coated tablet	60 tablets/30 days
		125 mg film-coated tablet	
generic bosentan		32 mg tablet for oral suspension	120 tablets/30 days
		62.5 mg film-coated tablet	60 tablets/30 days
		125 mg film-coated tablet	
macitentan (Opsumit)		10 mg tablet	30 tablets/30 days
riociguat (Adempas)	Chronic thromboembolic pulmonary hypertension (CTEPH); Pulmonary arterial hypertension (PAH)	0.5 mg tablets	90 tablets/30 days
		1 mg tablets	
		1.5 mg tablets	
		2 mg tablets	
		2.5 mg tablets	
iloprost (Ventavis)	Pulmonary arterial hypertension (PAH)	10 mcg/mL inhalation solution ampule	9 cartons of 30 ampules per 30-day supply
		20 mcg/mL inhalation solution ampule	
treprostinil (Tyvaso)	Pulmonary arterial hypertension (PAH); Pulmonary hypertension (PH) Due to Interstitial Lung Disease (ILD)	1.74 mg/2.9 mL inhalation solution ampule	1 Inhalation System Starter Kit (28 ampule carton)/ 1st 28 days of initiation therapy 1 Inhalation System Refill Kit (28 ampule carton)/28 days 7 Four Pack Cartons with one foil pouch containing four 2.9 mL ampules/28 days
		Maintenance Kit	

treprostinil (Tyvaso DPI)	Pulmonary arterial hypertension (PAH)	16 mcg cartridge	112 cartridges/28 days
		Maintenance Kit 32 mcg cartridge	
		Maintenance Kit 48 mcg cartridge	
		Maintenance Kit 64 mcg cartridge	
		Maintenance Kit 32 mcg & 48 mcg	224 cartridges/28 days
		Titration Kit 16 mcg & 32 mcg	196 cartridges/28 days
		Titration Kit 16 & 32 & 48 mcg	252 cartridges/28 days
treprostinil (Remodulin)		5 mg/mL injection solution	up to 50 ng per kg per minute subcutaneously or intravenously
		10 mg/mL injection solution	
		20 mg/20 mL injection solution	
		50 mg/20 mL injection solution	
		100 mg/20 mL injection solution	
		200 mg/20 mL injection solution	
treprostinil (Orenitram)		0.125 mg ER tablet	90 extended-release oral tablets/30 days
		0.25 mg ER tablet	
		1 mg ER tablet	
		2.5 mg ER tablet	
		5 mg ER tablet	
selexipag (Uptravi)		200 mg	140 oral use tablets/28 days
		400 mg	

		600 mcg	Titration pack (140 count – 200mcg oral use tablets + 60 count – 800mcg) 60 oral use tablets/30 days
		800 mcg	
		1000 mcg	
		1200 mcg	
		1400 mcg	
		1600 mcg	
sotatercept (Winrevair)	Pulmonary arterial hypertension (PAH)	45 mg injection kit	1 kit/21 days
		60 mg injection kit	
Macitentan/tadalafil (Opsynvi)	Pulmonary arterial hypertension (PAH)	10 mg/20 mg tablet	30 tablets/30 days
		10 mg/40 mg tablet	

Initial Evaluation

I. **Ambrisentan (Letairis), generic ambrisentan, bosentan (Tracleer), generic bosentan, macitentan (Opsumit), macitentan/tadalafil (Opsynvi), riociguat (Adempas), iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso, Tyvaso DPI), treprostinil (Orenitram), treprostinil injection (Remodulin), selexipag (Uptravi), and sotatercept (Winrevair)** may be considered medically necessary when the following criteria below are met:

A. Member is 18 years of age or older; **OR**

1. Member is three years of age or older and request is for bosentan (generic, Tracleer); **AND**

B. Medication is prescribed by, or in consultation with, cardiologist or pulmonologist; **AND**

C. A diagnosis of one of the following:

1. **Pulmonary arterial hypertension (PAH) (WHO Group 1)**; **AND**

a. An acute vasoreactivity test has been performed; **AND**

i. Results were negative; **OR**

ii. Results were positive; **AND**

1. Treatment with a calcium channel blocker (CCB) (e.g. amlodipine, diltiazem, felodipine, nifedipine, nicardipine, or verapamil) has been ineffective after three months of therapy, unless contraindicated, or not tolerated; **AND**

b. The request is for generic ambrisentan, generic bosentan, macitentan (Opsumit), or riociguat (Adempas); **OR**
    i. The request is for brand ambrisentan (Letairis); **AND**
        1. Generic ambrisentan has been ineffective, contraindicated, or not tolerated; **OR**
    ii. The request is for brand bosentan (Tracleer); **AND**
        1. Generic bosentan has been ineffective, contraindicated, or not tolerated; **OR**
    iii. The request is for macitentan/tadalafil (Opsynvi); **AND**
        1. The member has documented non-adherence to dual therapy with an ERA and a PDE-5 inhibitor (taken as individual components); **OR**
c. The request is for iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso) inhalation solution, treprostinil dry powder inhalation (Tyvaso DPI), treprostinil (Orenitram) or selexipag (Uptravi); **AND**
    i. Treatment with TWO of the following groups has been ineffective, contraindicated, or not tolerated:
        1. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
        2. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil]
        3. riociguat (Adempas); **OR**
d. The request is for treprostinil injection solution; **AND**
    i. The request is for the generic treprostinil injection; **OR**
        1. Request is for brand Remodulin and generic treprostinil injection solution has been ineffective, contraindicated, or not tolerated; **AND**
    ii. Member has WHO functional class IV symptoms; **OR**
    iii. Member has WHO functional class III symptoms and is classified as high risk (poor prognosis) [*see appendix table 1*]; **OR**
        1. The member has WHO functional class III symptoms and is classified as low risk (good prognosis); **AND**
            a. Treatment with TWO of the following groups has been ineffective, contraindicated, or not tolerated:
                i. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
                ii. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil]

iii. riociguat (Adempas); **OR**

iv. Member is transitioning from epoprostenol to treprostinil (Remodulin); **OR**

e. The request is for sotatercept (Winrevair); **AND**

i. Member has WHO functional class II or III symptoms; **AND**

ii. Provider attestation that the member has, or will receive, training from a healthcare professional on how to reconstitute, prepare, measure, and inject sotatercept (Winrevair); **AND**

iii. Treatment with one agent in each of the following groups has been ineffective, contraindicated, or not tolerated:

1. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
2. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil] or riociguat (Adempas)
3. Prostacyclin agonist [e.g., treprostinil (Remodulin, Tyvaso, Orenitram), selexipeg (Uptravi)]; **AND**

iv. Provider attestation that the member will be continuing background therapy with at least two other PAH medications, unless contraindicated or not tolerated; **OR**

2. **Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4)**; **AND**

i. Member has inoperable CTEPH; **OR**

ii. Member had a surgery for CTEPH performed; **AND**

iii. The request is for riociguat (Adempas); **OR**

3. **Pulmonary Hypertension (PH) Due to Interstitial Lung Disease (ILD) (WHO Group 3); AND**

i. Diagnosis confirmed with chest high-resolution computed tomography (HRCT) imaging**; AND**

ii. Diagnosis confirmed with a right heart catheterization (RHC)**; AND**

iii. Member does NOT have PH caused by obstructive lung disease (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis) or hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation); **AND**

iv. The request is for treprostinil (Tyvaso) inhalation solution or treprostinil dry powder inhalation (Tyvaso DPI)

II. Ambrisentan (Letairis) is considered investigational when used for all other conditions including but not limited to:

A. Chronic thromboembolic pulmonary hypertension (CTEPH)

B. Digital ulcers in systemic sclerosis
C. Lowering Portal Pressure in Patients with Liver Cirrhosis
D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
E. Sarcoidosis

III. Bosentan (Tracleer) is considered investigational when used for all other conditions including but not limited to:
A. Chronic obstructive pulmonary disease - Pulmonary hypertension
B. Chronic thromboembolic pulmonary hypertension (CTEPH)
C. Digital ulcers in systemic sclerosis
D. Essential hypertension
E. Raynaud phenomenon in systemic sclerosis
F. Thromboembolic pulmonary hypertension, chronic

IV. Macitentan (Opsumit) is considered investigational when used for all other conditions including but not limited to:
A. Chronic thromboembolic pulmonary hypertension (CTEPH)
B. Digital ulcers in systemic sclerosis
C. Glioblastoma

V. Riociguat (Adempas) is considered investigational when used for all other conditions including but not limited to:
A. Systemic sclerosis-associated digital ulcers

VI. Treprostinil (Tyvaso; Tyvaso DPI) is considered investigational when used for all other conditions including but not limited to:
A. Pulmonary hypertension (PH) WHO Groups II-V
- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III – Chronic obstructive pulmonary disease (COPD), bronchiectasis; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V - Sarcoidosis

B. Chronic thromboembolic pulmonary hypertension (CTEPH)

VII. Iloprost (Ventavis), treprostinil (Orenitram, Remodulin) and selexipag (Uptravi) are considered investigational when used for all other conditions, including but not limited to:
A. Pulmonary hypertension (PH) WHO Groups II-V
- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed

obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

B. Chronic thromboembolic pulmonary hypertension (CTEPH)

VIII. Sotatercept (Winrevair) is considered investigational when used for all other conditions including but not limited to:
A. Pulmonary hypertension (PH) WHO Groups II-V
- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

B. Chronic thromboembolic pulmonary hypertension (CTEPH)
C. Newly diagnosed PH (i.e., treatment naïve)
D. Myeloproliferative disorders/Myelofibrosis
E. Anemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g. improved exercise capacity and tolerance, reduced number of hospitalizations, improvement in WHO functional class)

Supporting Evidence

I. Patients with PH are classified into five clinical groups based on cause of PH.
a. Group 1: pulmonary **arterial** hypertension (PAH) which has several causes (e.g., inheritable causes, drugs, connective tissue disease)
b. Group 2: PH due to left-sided heart disease
c. Group 3: PH due to chronic lung disorders and hypoxemia
d. Group 4: PH due to pulmonary artery obstructions
e. Group 5: PH due to unidentified mechanisms

II. The safety and efficacy of bosentan (Tracleer) in pediatric patients was evaluated in an open-label, uncontrolled study with 19 pediatric PAH patients aged 3 to 15 years. Patients had primary pulmonary hypertension (n = 10) or PAH related to congenital heart diseases (9 patients) and were WHO functional class II or class III at baseline. Patients were dosed with bosentan for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. Hemodynamics were measured in 17 patients. The mean decrease in (pulmonary vascular resistance) 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.

*Normal PVR value is <250 dyn·sec·cm$^{-5,}$ but PAH patients, depending on the severity of the disease state, have a significantly higher PVR value. A Systematic Review and Meta-Analysis of 12 studies was done and baseline PVR value of the PAH patients included in the study was 668.6±219.1 <250 dyn·sec·cm^{-5}.

III. Clinical studies of ambrisentan (Letairis), macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), and selexipag (Uptravi) did not include patients younger than 18 years to determine whether they respond differently from older patients. Safety and efficacy in pediatric patients have not been established.

IV. Pulmonary Hypertension (PH0 is a progressive and life-threatening disease. The medications as well as the disease state should be managed by a specialist.

PAH

V. The American College of Chest Physicians (CHEST) guideline for Therapy for PAH in adults suggests that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a medical center with experience in the performance and interpretation of vasoreactivity testing. Contraindications to acute vasoreactivity testing include low systemic BP, low CO, or the presence of FC IV symptoms. Patients who demonstrate acute vasoreactivity – in the absence of right-sided heart failure or contraindications to CCB therapy – according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB. CCBs are considered primary therapy.

VI. Lacking head-to-head comparisons of pharmacologic agents for the treatment of PAH, there is insufficient evidence to determine if one agent is superior to another.

VII. Ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), and tadalafil/macitentan (Opsynvi) are indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adults to improve exercise ability and decrease clinical worsening.

a. Studies with bosentan (Tracleer) establishing effectiveness included predominantly patients with WHO 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 heart disease with left-to-right shunts (18%). The primary study endpoint was 6-minute walk distance; however, symptoms and functional status was also assessed. In both trials, treatment with Tracleer resulted in a significant increase in exercise ability. The improvement in walk distance was apparent after 1 month of treatment and fully developed by about 2 months of treatment.

b. Ambrisentan (Letairis) and macitentan (Opsumit) effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients who were included in this study had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), or PAH caused by congenital heart disease with repaired shunts (8%). The primary study endpoint was a 6-minute walk distance. An increase in 6-minute walk distance was observed after 4 weeks of treatment with Letairis, with a dose-response observed after 12 weeks of treatment.

c. Macitentan (Opsumit) effect on progression of PAH was demonstrated in a multi-center, long-term, placebo-controlled study in 742 patients with symptomatic PAH WHO FC II-IV. The primary study endpoints were time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy), lung transplantation, initiation of IV or subcutaneous (SC) prostanoids, or "other worsening of PAH" during double-blind treatment plus 7 days. Other worsening was defined as all of the following: a sustained ≥15% decrease from baseline in 6MWD, worsening of PAH symptoms (worsening of WHO FC), and need for additional treatment for PAH. All of these other worsening events were confirmed by an independent adjudication committee, blinded to treatment allocation. Treatment with OPSUMIT 10 mg resulted in a 45% reduction in the occurrence of the primary endpoint.

d. Tadalafil/macitentan (Opsynvi) was studied in one Phase 3, randomized, double-blind, active controlled trial against tadalafil or macitentan as monotherapy in 187 PAH patients with WHO FC II or III symptoms. The primary endpoint was change in PVR at week 16, and a statistically significant improvement was demonstrated in the tadalafil/macitentan (Opsynvi) over both monotherapy arms. Key secondary outcome of change in 6MWD did not meet the threshold for statistical significance, and other key secondary outcomes of cardiopulmonary and cardiovascular symptom score, and absence of worsening in WHO FC were not able to be formally tested for statistical significance due to hierarchical testing methods. No new safety signals emerged during the clinical trial, although incidence of adverse events was higher in the tadalafil/macitentan (Opsynvi) arm; this is likely due to combination therapy, which is commonly utilized in real world clinical practice.

    i. There are no head-to-head trials comparing the safety and efficacy tadalafil/macitentan (Opsynvi) to dual combination therapy with an ERA and PDE-5 inhibitor, taken as individual components, although any differences are anticipated to be negligible. Since the main driver of transition to tadalafil/macitentan (Opsynvi) would be patient preference for a single combination tablet compared to three (or more) tablets, documented non-adherence to dual therapy regimen (taken as individual components) would be the only acceptable clinical rationale for tadalafil/macitentan (Opsynvi).

VIII. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), treprostinil (Remodulin), and selexipag (Uptravi) are synthetic analogs of prostacyclin indicated for the treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms

(WHO Class), and lack of deterioration. Injectable treprostinil (Remodulin) also carries FDA approval for transition from epoprostenol.

IX. Studies in Iloprost (Ventavis) establishing effectiveness included predominately patients with WHO Functional Class III-IV symptoms, etiologies of idiopathic or heritable PAH (65%), or PAH associated with connective tissue diseases (23%). The primary efficacy endpoint was clinical response at 12 weeks with a composite endpoint defined by: improvement in exercise ability (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing, improvement with at least one WHO FC versus baseline, and no death or deterioration of pulmonary hypertension. The percentage of patients who had a minimum increase of at least 10 percent in the distance walked within six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group. The absolute change in the 6MWD was significantly larger in the iloprost group. More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the WHO FC.

X. Studies in treprostinil (Tyvaso) to establish effectiveness included predominately patients with WHO Functional Class III symptoms, etiologies of idiopathic or heritable PAH (56%), or PAH associated with connective tissue diseases (33%). While there is long-term data on use of treprostinil (Tyvaso) by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil (Tyvaso) has been on a background of bosentan (Tracleer) (an endothelin receptor antagonist) or sildenafil (Revatio) (a phosphodiesterase type 5 inhibitor).

XI. Per the package insert, the study in treprostinil (Orenitram), that established effectiveness included predominately patients with WHO functional class II-III symptoms, etiologies of idiopathic or heritable PAH (75%), or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of treprostinil (Orenitram) on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

XII. Treprostinil injection (Remodulin) is indicated for subcutaneous or intravenous use only as a continuous infusion. The package insert states treprostinil injection is preferably infused subcutaneously but can be administered by a central intravenous line if the subcutaneous route is not tolerated. Treprostinil can be self-administered subcutaneously by continuous infusion, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. 2019 CHEST guidelines recommend use of treprostinil injection (Remodulin) for patients with continued progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents; or in patients with WHO functional class IV.

XIII. The effectiveness of selexipag (Uptravi) was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

XIV. The safety and efficacy of sotatercept (Winrevair) was studied in the Phase 3, randomized, double-blind, placebo-controlled STELLAR trial in 323 adult patients with WHO group 1 PAH with functional class (FC) II or III symptoms over a period of 24 weeks. Patients continued their stable background therapy consisting of monotherapy, dual therapy, or triple therapy with medications that were available at the time of study enrollment, depending on the patient's disease severity.

Approximately 60% of patients were receiving triple therapy with an PDE-5 inhibitor, ERA, and prostacyclin agonist, with nearly 40% receiving prostacyclin infusion therapy at inclusion. The primary efficacy outcome was the change in the 6-minute walk distance (6MWD) from baseline to week 24. Key secondary endpoints consisted of a multicomponent improvement at week 24 compared to baseline, and change from baseline in pulmonary vascular resistance, NT-proBNP level, and improvement in WHO functional class at week 24. All primary and key secondary endpoints met the threshold for statistical significance compared to placebo.

XV. While this was a well-designed randomized, double-blind, placebo-controlled trial with sotatercept (Winrevair) demonstrating statistical significance in the key primary and secondary endpoints, the trial utilized a surrogate endpoint as the primary endpoint and an unvalidated key secondary endpoint (MCI) that have not been shown to correlate with impact on morbidity/mortality. However, the positive impact on WHO-FC and 6MWD may be considered clinically meaningful for patients' functionality and quality of life. Based on this information, the overall quality of evidence is considered moderate. Additionally, the trial duration was limited to 24 weeks, the durability of response in this chronic disease state remains unknown and will be realized in real-world settings.

XVI. The SOTERIA trial is an ongoing, long-term (7-year) open label follow-up study of patients who completed the initial phase 2 PULSAR or Phase 3 STELLAR clinical trial; all patients were continued or were initiated on sotatercept (Winrevair), if they were originally in the placebo arm. The interim one-year follow-up data suggests that there may be maintenance benefit in the 6MWD, NT-proBNP, and WHO-FC compared with study baseline, although there was a large variance around the mean for the 6MWD and NT-proBNP outcomes. Final readout of this data is anticipated around September 2027.

XVII. Most of the adverse events reported during the clinical trial were mild to moderate in severity, and fewer patients in the sotatercept (Winrevair) group (8.0%) experienced severe adverse events (AEs) compared to placebo (13.1%). The most common AEs reported during the clinical trial period for sotatercept (Winrevair) versus placebo, respectively, included thrombocytopenia (6.1% vs. 2.5%), bleeding events (21.5% vs. 12.5%), headache (20.2% vs. 15%), nausea (9.8% vs. 11.2%), telangiectasia (10.4% vs. 3.1%), and dizziness (10.4% vs. 1.9%). A total of nine patients died through the data cut-off date: two patients (1.2%) in the sotatercept group due to acute myocardial infarction and intracranial hemorrhage, and seven patients (4.4%) in the placebo group due to cardiac arrest, cardiogenic shock, right ventricular failure, sepsis, PAH, and COVID.

XVIII. The American College of Cardiology (ACCF)/American Heart Association (AHA) guidelines indicate oral ERA or PDE-5 inhibitor therapy as first line treatment for lower risk PAH patients. There is insufficient safety and efficacy evidence to establish that any one oral therapy for PAH is clearly superior to another. Treatment guidelines support combination therapy of PDE, ERA, and prostanoid agents.

XIX. For patients with WHO functional class II or III 2019 American College of Chest Physicians (CHEST) guidelines recommend the combination of ambrisentan and tadalafil as first line therapy. This is based on data from the AMBITION trial. The trial involved 605 patients with WHO functional class II or III PAH. Patients were randomly assigned to receive once daily ambrisentan plus tadalafil or to either drug alone. Doses were titrated from 5-10 mg/day for

ambrisentan and from 20-40 mg/day for tadalafil. Treatment with the combination was associated with an approximately 50% reduction in risk for clinical failure compared with either drug alone (*P* = .0002), with improved exercise ability as well as decreased disease progression and hospitalization.

XX. The 2019 CHEST guidelines recommend treatment naive PAH patients with WHO functional class II and III use combination therapy with ambrisentan and tadalafil to improve 6MWD. For patients who are unwilling or unable to tolerate combination therapy monotherapy with a currently approved ERA, PDE-5 inhibitor, or the soluble guanylate cyclase stimulator riociguat is advised. Guidelines suggest that parenteral or inhaled prostanoids may be chosen as initial therapy, in combination with tadalafil and ambrisentan, for treatment naive PAH patients with WHO FC III symptoms who present with a more severe phenotype, or as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals on established dual therapy.

CTEPH

XXI. Riociguat (Adempas) is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) after surgical treatment, inoperable CTEPH or PAH to improve exercise capacity and WHO functional class. Medical therapy prior to surgery is not indicated because there is no evidence to show it improves hemodynamic or mortality outcomes after surgery.

PH due to ILD

XXII. WHO Group 3 PH can be further broken down to specific causes. Those causes are:

- Obstructive lung disease (e.g., COPD or bronchiectasis)
- Restrictive lung disease (e.g., ILD, kyphoscoliosis)
    - Other lung disease with mixed obstruction and restriction (eg, pulmonary fibrosis with emphysema)
- Hypoxia without lung disease (e.g., high altitude, sleep apnea, obesity hypoventilation)
- Developmental lung disorders (e.g., bronchopulmonary dysplasia, congenital lobar emphysema)

XXIII. FDA approval for treprostinil (Tyvaso) is specific to PH associated with ILD as that was the population evaluated in clinical trials.

XXIV. The safety and efficacy of treprostinil (Tyvaso) inhalation solution for the treatment of patients with PH due to ILD was studied in a Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled trial.

a. Patients were adults with Group 3 pulmonary hypertension diagnosed by right heart catheterization. The mean age was 66.5 years, 46.9% were female and majority had the diagnosis of idiopathic interstitial pneumonia (in 44.8%).
b. Primary efficacy outcome measure of difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16 was met with a difference of 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001).
c. Clinical worsening was evaluated as a secondary endpoint and occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test)

d. There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance–saturation product at week 16
e. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo.

XXV. Patients who have shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy were excluded from the clinical trial. There is a lack of clinical trial data to show that Treprostinil (Tyvaso) would be effective or safe in this patient population.

Investigational Uses

I. Ambrisentan (generic, Letairis);
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
      a. AMBER I is a phase 3, randomized, double-blind, placebo controlled, parallel group, 16-week study evaluating the safety and efficacy of ambrisentan and placebo in subjects with inoperable CTEPH. AMBER II is an open-label, extension study of the long-term safety, tolerability, and efficacy.
      b. These studies were terminated early due to futility of enrollment. This was due to several factors, including an unexpectedly low screening rate (~20% of expected) and high screening failure rate (approaching 60%, mostly due to concerns regarding inoperability raised by the central adjudication committee).
   B. Digital ulcers (DU) in systemic sclerosis
      a. A pilot study was conducted to evaluate the efficacy of ambrisentan in the treatment and prevention of digital ulcers in patients with systemic sclerosis and they found that ambrisentan did not prevent the development of new DU over a 4-week time period after 24 weeks. A placebo-controlled study with more patients will be necessary to conclusively assess the effects of ambrisentan on DUs. There is no robust data to support the use of ambrisentan in DUs.
   C. Lowering Portal Pressure in Patients with Liver Cirrhosis
      a. A phase II, single-arm, open-label study to characterise the effect on portal pressure, the effect on renal function and the pharmacokinetic profile of ambrisentan in patients with decompensated cirrhosis is being conducted but no results have been published yet.
   D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
      a. A Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy and safety of ambrisentan in subjects with idiopathic pulmonary fibrosis and pulmonary hypertension called ARTEMIS-PH was terminated.
   E. Sarcoidosis
      a. Ambrisentan was studied for Sarcoidosis Associated Pulmonary Hypertension in a single group assignment, open-label clinical trial and suggested a possible benefit of this drug in selected patients. However, the study was a prospective, open-label, proof

of concept trial of ambrisentan that wasn't powered enough to show robust safety and efficacy data to support the use.

b. There is limited or no published clinical trial data to support the use of ambrisentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted either had very few patients, data was not published, or the studies were terminated.

II. Bosentan (Tracleer)

A. Chronic obstructive pulmonary disease - Pulmonary hypertension

a. In a 12-week randomized trial (N=30) in patients with severe, or very severe, COPD who did not have severe pulmonary hypertension at rest, there was no significant between-group difference in change from baseline in the mean 6-minute walking distance. Additionally, from baseline to week 12, the mean arterial partial pressure of oxygen significantly decreased in the bosentan group compared with placebo. Health-related quality of life scores (Short-Form-36 Health Survey) also significantly worsened in the bosentan group compared with placebo.

b. In a small, open-label study (N=32), addition of bosentan to best supportive care (BSC) improved the 6-minute walking distance and WHO functional class compared with patients receiving BSC alone. Bosentan plus BSC did not significantly improve baseline pulmonary volumes (functional vital capacity, forced expired volume in 1 second), cardiac index, arterial blood gases (partial pressure of oxygen and carbon dioxide), or quality of life (St. George questionnaire).

c. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline does not recommend use of bosentan for treating patients with severe COPD.

B. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

a. Bosentan was studied in a prospective, phase III, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability in 157 patients with inoperable CTEPH (NCT00313222). The primary outcome was change from baseline to week 16 in 6MWD and change from baseline to week 16 in pulmonary vascular resistance (PVR) at rest. A statistically significant treatment effect (TE) on PVR was demonstrated: -24.1% of baseline (95% confidence interval [CI]: -31.5% to -16.0%; $p < 0.0001$). Mean TE on 6-min walk distance was +2.2 m (95% CI: -22.5 to 26.8 m; $p = 0.5449$) which is not statistically significant.

b. The BENEFIT open-label, extension study in patients with inoperable CTEPH. In total, 148 of the patients who received randomized treatment rolled over into the extension. The trial data has not been published.

c. There is limited clinical trial data to support the use of bosentan in CTEPH. The clinical trial showed very limited efficacy and safety data.

C. Digital ulcers in systemic sclerosis

A. In a double-blind, placebo-controlled study, 122 patients with limited or diffuse systemic sclerosis, according to American College of Rheumatology criteria, and documented digital ulcer within the previous 12 months were randomized 2:1 to treatment with oral bosentan (79 patients) or placebo (43 patients). Mean patient age

was 51.8 years, and 63% of patients had digital ulcers at baseline. In patients receiving bosentan, the number of new digital ulcers was significantly reduced compared with placebo (*P*=0.0083), averaging 1.4 and 2.7 new ulcers per patient, respectively. Of patients with digital ulcers at baseline, an average of 1.8 new ulcers occurred per bosentan-treated patient and an average of 3.6 new ulcers occurred per placebo-treated patient, a reduction of 50% (*P*=0.0075). There was a slight improvement in Scleroderma Health Assessment Questionnaire (SHAQ) scores that did not reach statistical significance, except for hand function which was significantly improved in bosentan-treated patients. In patients with diffuse scleroderma with digital ulcers at baseline, 11% of bosentan-treated patients developed 4 or more new ulcers and 0% developed 7 or more new ulcers, compared with 50% and 20% of patients in the placebo group. There was no significant difference in time to complete or partial healing of ulcers between groups; however, there was a slight trend toward slower healing in patients treated with bosentan. Adverse effects of bosentan included diarrhea (7 [8.9%] patients) and elevated transaminase levels (9 [11.4%] patients). Five patients in the bosentan group withdrew because of abnormal liver function tests.

D. Essential hypertension
   a. There is no evidence that differentiates safety and efficacy of bosentan from other traditional medications (diuretics, CCB, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and alfa and beta blockers).

E. Raynaud phenomenon in systemic sclerosis
   a. Data from controlled and uncontrolled trials evaluating bosentan (Tracleer) in the management of secondary Raynaud phenomenon demonstrate conflicting results in clinical and microvascular assessments. According to evidence-based international consensus-derived recommendations, bosentan has no confirmed efficacy in the treatment of active digital ulcers in systemic sclerosis patients but is effective in the prevention of digital ulcers, particularly multiple ulcers, and should be considered after other therapies have failed.

F. Thromboembolic pulmonary hypertension, chronic
   a. A systematic review identified 2 randomized trials of 182 patients with chronic thromboembolic pulmonary hypertension that compared 16 weeks of treatment with bosentan (Tracleer) versus placebo. Bosentan (Tracleer) significantly improved the cardiopulmonary hemodynamic parameters of cardiac index and pulmonary vascular resistance. Bosentan (Tracleer) did not significantly affect the 6-minute walk distance, mean pulmonary arterial pressure, risk of functional class deterioration, or risk of clinical worsening. The risk of liver function abnormality was significantly increased with bosentan (Tracleer).

III. Macitentan (Opsumit);

A. Chronic thromboembolic pulmonary hypertension (CTEPH)
   a. The safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension were evaluated in MERIT-1 and MERIT-2:

i. MERIT-1 is a prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability in 80 patients. The primary efficacy endpoint is defined as the pulmonary vascular resistance (PVR) at rest at week 16 expressed as percent of baseline PVR at rest and the geometric mean PVR at rest decreased to 73·0% (95% CI 63·6–83·8) of the baseline value in the macitentan group, corresponding to a mean decrease from baseline of 206 dyn·s/cm^5, and decreased to 87·2% (95% CI 78·5–96·7) of the baseline value in the placebo group, corresponding to a mean decrease from baseline of 86 dyn·s/cm^5 (ratio of geometric means 0·84, 95% CI 0·70–0·99, p=0·041). The trial did not include patients from the United States of America, included a small patient population and was short term.

ii. MERIT-2 is an ongoing, long-term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess safety, tolerability and efficacy. Results from this trial have not been reported at this time.

b. There is insufficient clinical trial data to support the use of macitentan in patients with CTEPH. Clinical trials are ongoing to further evaluate macitentan for CTEPH.

B. Digital ulcers in systemic sclerosis

a. A prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis was terminated.

b. Two international, randomized, double-blind, placebo-controlled trials (DUAL-1, DUAL-2) were conducted in patients with systemic sclerosis and active digital ulcers at baseline. The primary outcome for each trial was the cumulative number of new digital ulcers from baseline to week 16. The results of the studies do not support the use of macitentan for the treatment of digital ulcers in this patient population.

C. Glioblastoma

a. A single-center, open-label, phase 1 study of concurrent therapy with macitentan, radiotherapy, and temozolomide, followed by maintenance therapy with macitentan and temozolomide in subjects with newly diagnosed glioblastoma was terminated due to low recruitment.

b. A Phase 1/1b, open-label study in patients with recurrent glioblastoma to assess the safety and tolerability of macitentan in combination with dose-dense temozolomide was terminated because the results did not clearly support continuing development in recurrent GBM.

c. There is limited or no published clinical trial data to support the use of macitentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, terminated, or data was not published.

IV. Riociguat (Adempas);

A. Systemic sclerosis-associated digital ulcers

a. Seventeen participants (eight placebo, nine riociguat) were randomized at five centers. Baseline characteristics were comparable between the treatment groups, except for participants who were randomized to placebo were older and had longer disease duration. Treatment with riociguat did not reduce the number of DU net burden compared with placebo at 16 weeks. Open-label extension suggests that longer duration is needed to promote DU healing, which needs to be confirmed in a new trial.
b. The conducted trials are not powered enough and show low or no efficacy. There is limited to no published clinical trial data to support the use of riociguat (Adempas) in conditions other than persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or Pulmonary Arterial Hypertension (PAH).

IX. Treprostinil (Tyvaso; Tyvaso DPI);
A. Pulmonary hypertension (PH) WHO Groups II-V
- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III – Non-ILD lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis; Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema); Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

There is limited or no published clinical trial data to support the use of treprostinil (Tyvaso) in conditions other than PAH and PH due to ILD. The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

X. Iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi);
A. Pulmonary hypertension (PH) WHO Groups II-V
- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

B. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

IV. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi);
A. Chronic thromboembolic pulmonary hypertension (CTEPH) – WHO Group IV
a. There is insufficient data to support the use of selexipag (Uptravi) in patients with inoperable or persistent/recurrent after surgical and/or interventional treatment CTEPH. Clinical trial was terminated as the study did not demonstrate efficacy on the primary endpoint, PVR vs. placebo at wk 20 at a planned interim analysis.

b. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

Appendix

I. Table 1: PAH Determinants of Prognosis (ACCF/AHA Guidelines)

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO2 greater than 10.4 mL/kg/min	Peak VO2 less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m2	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m2
BNP§	Minimally elevated	Significantly elevated
*Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions.		
†WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.		
‡6MW distance is also influenced by age, gender, and height.		
§As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.		

6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.

References

1. Ambrisentan (Letairis®) [Prescribing Information]. Gilead Sciences, Inc., Foster City, CA. 04/23/2019
2. Bosentan (Tracleer®) [Prescribing Information]. Actelion Pharmaceuticals US, Inc. South San Francisco, CA. June 2015
3. Macitentan (Opsumit®) [Prescribing Information]. Actelion Pharmaceuticals US, Inc. South San Francisco, CA. 04/23/2019
4. Riociguat (Adempas) [package insert].Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2013.
5. Iloprost (Ventavis®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 10/16/2017
6. Treprostinil (Tyvaso®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 03/2021
7. Treprostinil (Orenitram®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 01/24/2017
8. Selexipag (Uptravi®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 09/04/2019
9. Barst RJ, Ivy D, Dingemanse J, Widlitz A, Schmitt K, Doran A, Bingaman D, Nguyen N, Gaitonde M, van Giersbergen PL. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. (n.d.). Clinical Pharmacology & Therapeutics, 73(4), 372–382. doi: https://doi.org/10.1016/S0009-9236(03)00005-5 https://www.ncbi.nlm.nih.gov/pubmed/12709727
10. Berger RM, Haworth SG, Bonnet D, Dulac Y, Fraisse A, Galiè N, Ivy DD, Jaïs X, Miera O, Rosenzweig EB, Efficace M, Kusic-Pajic A, Beghetti M. FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the pediatric Formulation of bosentan in pulmonary arterial hypertension. Int J Cardiol. 2016 Jan 1;202:52-8. doi: 10.1016/j.ijcard.2015.08.080 https://www.ncbi.nlm.nih.gov/pubmed/26386921
11. Galie N, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl): D60-72.
12. Taichman DB, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. CHEST 2019 Aug; 146(2). 449-75.
13. Galie N, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl): D60-72.
14. McLaughlin VV, Archer SL, et al. Accf/aha 2009 expert consensus document on pulmonary hypertension: a report of the american college of cardiology foundation task force on expert consensus documents and the american heart association: developed in collaboration with the american college of chest physicians, american thoracic society, inc. , and the pulmonary hypertension association. Circulation. 2009;119(16):2250-2294.
15. Galie, Nazzareno MD; Olschewski, Horst MD; Oudiz, Ronald J. MD; Torres, Fernando MD. 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. 117(23), 10 June 2008. DOI: 10.1161/CIRCULATIONAHA.107.742510 PMID: 18506008
16. K Ahmadi-Simab;P Lamprecht;B Hellmisch. Treatment of pulmonary arterial hypertension (PAH) with oral endothelin-receptor antagonist bosentan in systemic sclerosis: BREATHE-1 trial and clinical experience. 63(6). 495-497. DOI: 10.1007/s00393-004-0594-3 PMID: 15605216
17. N. Channick MD; Marion Delcroix MD; Hossein-Ardeschir Ghofrani MD; Elke Hunsche PhD. Effect of Macitentan on Hospitalizations: Results from the SERAPHIN Trial. January 2015. 3(1). 1-8. https://doi.org/10.1016/j.jchf.2014.07.013

18. Horst Olschewski, M.D., Gerald Simonneau, M.D., Nazzareno Galiè, M.D., Timothy Higenbottam, M.D. et. Inhaled Iloprost for Severe Pulmonary Hypertension. New England Journal of Medicine 2002; 347:322-329 DOI: 10.1056/NEJMoa020204 PMID: 25457902
19. Wilkins, MR, Paul, GA, Strange, JW, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. Am J Respir Crit Care Med. 2005 Jun 1;171(11):1292-7. PMID: 15750042
20. Korn JH, Mayes M, Matucci Cerinic M, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004;50(12):3985-3993.[PubMed 15593188]
21. Chen X, Zhai Z, Huang K, et al: Bosentan therapy for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: a systemic review and meta-analysis. Clin Respir J 2018; 12(6):2065-2074. PubMed Abstract: http://www.ncbi.nlm.nih.gov/... PubMed Article: http://www.ncbi.nlm.nih.gov/...
22. Gilead Sciences. ARTEMIS-PH - Study of Ambrisentan in Subjects With Pulmonary Hypertension Associated With Idiopathic Pulmonary Fibrosis (ARTEMIS-PH). ClinicalTrials.gov Identifier: NCT00879229
23. Noorik Biopharmaceuticals AG. A Study Evaluating the Utility of Ambrisentan in Lowering Portal Pressure in Patients with Liver Cirrhosis. ClinicalTrials.gov Identifier: NCT03827200
24. Medical University of South Carolina, Gilead Sciences. Ambrisentan (Letairis) for Sarcoidosis Associated Pulmonary Hypertension. ClinicalTrials.gov Identifier: NCT00851929
25. Judson MA, Highland KB, Kwon S, Donohue JF, Aris R, Craft N, Burt S, Ford HJ. Ambrisentan for sarcoidosis associated pulmonary hypertension. Sarcoidosis Vascular Diffuse Lung Dis. 2011 Oct; 28(2):139-45. PMID: 22117505
26. Chung L, Ball K, Yaqub A, Lingala B, Fiorentino D. Effect of the endothelin type A-selective endothelin receptor antagonist ambrisentan on digital ulcers in patients with systemic sclerosis: results of a prospective pilot study. J Am Acad Dermatol. 2015. 71(2): 400–401. doi: 10.1016/j.jaad.2014.04.028 PMID: 25037794
27. Actelion. Macitentan for the Treatment of Digital Ulcers in Systemic Sclerosis Patients (DUAL-2). ClinicalTrials.gov Identifier: NCT01474122
28. Dinesh Khanna, MD; Christopher P. Denton, MD; Peter A. Merkel, MD; et al. Effect of Macitentan on the Development of New Ischemic Digital Ulcers in Patients With Systemic Sclerosis DUAL-1 and DUAL-2 Randomized Clinical Trials. JAMA. 2016; 315(18):1975-1988. doi:10.1001/jama.2016.5258
29. Actelion. Clinical Study on Macitentan, RT and TMZ Concurrent Therapy Followed by Maintenance Macitentan and TMZ in Newly Diagnosed Glioblastoma. ClinicalTrials.gov Identifier: NCT02254954
30. Actelion. Clinical Study on the Safety and Tolerability of Macitentan in Combination with Dose-dense Temozolomide in Patients with Recurrent Glioblastoma. ClinicalTrials.gov Identifier: NCT01499251
31. Nagaraja V, Spino C, Bush E, Tsou PS, Domsic RT, Lafyatis R, Frech T, Gordon JK, Steen VD, Khanna D. A multicenter randomized, double-blind, placebo-controlled pilot study to assess the efficacy and safety of riociguat in systemic sclerosis-associated digital ulcers. Arthritis Res Ther. 2019 Sep 3; 21(1):202. doi: 10.1186/s13075-019-1979-7.
32. Up-to-Date. Treatment of Pulmonary Hypertension in Adults. Accessed via: http://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-inadults?source=machineLearning&search=pulmonary+hypertension&selectedTitle=2%7E150&sectionRank=2&anchor=H35#H35 on January 13, 2016.
33. Valerio G, Bracciale P, & Grazia D'Agostino A: Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. Ther Adv Respir Dis 2009; 3(1):15-21.
34. Aaron Waxman, M.D., Ph.D., et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med 2021; 384:325-334 DOI: 10.1056/NEJMoa2008470
35. Ganesh Raghu, et al. Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018. 198, 5. e44–e68, DOI: 10.1164/rccm.201807-1255ST
36. Klinger JR, Elliott CG, 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.
37. Remodulin[treprostinil) [package insert] United Therapeutics Corp; Research Triangle Park, NC. Revised July 2018
38. Tyvaso DPI [treprostinil) [package insert] United Therapeutics Corp; Research Triangle Park, NC. Revised May 2022
39. Winrevair. Package Insert. Merck Sharp & Dohme LLC; March 2024.
40. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2023;388(16):1478-1490. doi:10.1056/NEJMoa2213558

41. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2022); 43:3618-3731.
42. Klinger JR, Elliott G, 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.
43. Lin GA, Whittington MD, Nikitin D, Nhan E, Richardson M, Pearson SD, Rind DM. Sotatercept for Pulmonary Arterial Hypertension: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, November 14, 2023. Available from: https://icer.org/assessment/pulmonary-arterial-hypertension-2023/
44. Sotatercept (Winrevair) product dossier. Merck & co., Inc. March 2024.
45. Center for Drug Evaluation and Research. Application Number 761363Orig1s000 Integrated Review. Integrated Review: BLA761363. Updated 03/26/2024.
46. Gruning E, Jansa P, Fan F, et al. Randomized Trial of Macitentan/Tadalafil Single-Tablet Combination Therapy for Pulmonary Arterial Hypertension. J Am Coll Cardiol 2024; 83: 473-484.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added tadalafil/macitentan (Opsynvi) in the setting of group 1 PAH; Updated supporting evidence, references.	09/2024
Added sotatercept (Winrevair) in the setting of group 1 PAH; Updated supporting evidence	08/2024
Added Tyvaso DPI product. In the setting of PAH: Updated oral and inhaled prostoninoids (e.g., treopostinil) to require previous trial of two within a PDE-5, ERA, or riociguat. Removed requirement of a PDE-5 prior to approval of an ERA. Updated initial approval duration to be 6 months for all products.	04/2023
• **Added new indication of PH due to ILD for treprostinil (Tyvaso)** • **Added treprostinil injection (Remodulin) into policy** • **Removed requirement of PDE-5 monotherapy for 3 months in those requesting generic ambrisentan in combination with a PDE-5** • Added requirement of prior endothelin receptor antagonist if requesting Ventavis or Tyvaso in PAH	**06/2021**
• Updated renewal section with standard renewal language • Added chronic thromboembolic pulmonary hypertension (CTEPH) as an investigational indication to bosentan (generic, Tracleer), ambrisentan (generic, Letairis), macitentan (Opsumit) and selexipag (Uptravi)	03/2020

• Updated the criteria into policy format
• Added acute vasoreactivity test criteria to apply to all agents
• Added age limit to reflect clinical trial data
• Combined criteria for bosentan (generic, Tracleer), ambrisentan (generic, Letairis)& macitentan (Opsumit) with riociguat (Adempas) criteria and Iloprost (Ventavis), treprostinil (Tyvaso and Orenitram), selexipag (Uptravi)
• Quantity limit change iloprost (Ventavis) and bosentan (Letairis) to reflect the dosing in the package insert
• Treprostinil (Orenitram) 5mg doseage form added
• Added criteria because generic bosentan and generic ambrisentan became available we are driving patients to a more cost effective option;
  ○ Prior to getting bosentan (Tracleer), member has tried generic bosentan and treatment has been ineffective, contraindicated, or not tolerated
  ○ Prior to getting ambrisentan (Letairis), member has tried generic ambrisentan and treatment has been ineffective, contraindicated, or not tolerated
• Added generic bosentan and generic ambrisentan to the policy
	12/2019

• Added Uptravi for P&T 5/4/16 • Reviewed policy	3/29/2016
• Updated formatting. • Added Tyvaso and Orenitram, removed question regarding initial 6 minute walking distance and required trial and failure of generic sildenafil only for oral prostanoid.	03/17/2016

• Criteria update: Validated place in therapy and recommendations. • Removed questions regarding contraindications, warnings/precautions. • Updated header, footer and formatting [riociguat (Adempas)] • Reviewed	03/14/2016
Policy created and effective [iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)]	Prior to 3/17/2016 (no date available)
Policy created [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2016
Previously reviewed [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2014, 03/2016
Criteria for ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit) created	01/2013