Pulmonary Arterial 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.

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.

Length of Authorization

- Initial:
  i. Ambrisentan (generic, Letairis), bosentan (generic, Tracleer), and macitentan (Opsumit): Three months
  ii. Riociguat (Adempas), iloprost (Ventavis), treprostinil inhalation (Tyvaso), treprostinil tablet (Orenitram), treprostinil injection (Remodulin) and selexipag (Uptravi)]: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
ambrisentan (Letairis)	5 mg tablets	Pulmonary arterial hypertension (PAH)	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)	0.5 mg tablets	Chronic thromboembolic pulmonary hypertension (CTEPH); Pulmonary arterial hypertension (PAH)	90 tablets/30 days
	1 mg tablets		
	1.5 mg tablets		
	2 mg tablets		
	2.5 mg tablets		
iloprost (Ventavis)	10 mcg/mL inhalation solution ampule	Pulmonary arterial hypertension (PAH)	9 cartons of 30 ampules per 30 day supply
	20 mcg/mL inhalation solution ampule		
treprostinil (Tyvaso)	1.74 mg/2.9 mL inhalation solution ampule	Pulmonary arterial hypertension (PAH); Pulmonary hypertension (PH) Due to Interstitial Lung Disease (ILD)	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
treprostinil (Remodulin)	5 mg/mL injection solution	Pulmonary arterial hypertension (PAH)	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 mcg		140 oral use tablets/28 days
	400 mcg		Titration pack (140 count – 200mcg oral use tablets + 60 count – 800mcg) 60 oral use tablets/30 days
	600 mcg		
	800 mcg		
	1000 mcg		
	1200 mcg		
	1400 mcg		
	1600 mcg		

Initial Evaluation

I. Ambrisentan (Letairis), generic ambrisentan, bosentan (Tracleer), generic bosentan, macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso) inhalation solution, treprostinil (Orenitram), treprostinil injection (Remodulin), and selexipag (Uptravi) 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 with WHO Functional Class II-IV symptoms); **AND**

a. An acute vasoreactivity test has been performed; **AND**
   i. Results were negative; **OR**
   ii. Results were positive; **AND**
      a) 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. Treatment with a phosphodiesterase type-5 (PDE-5) inhibitor [e.g. sildenafil 20 mg three times daily or tadalafil 40 mg daily] has been ineffective after three months of therapy, contraindicated, or not tolerated; **OR**
   i. The request is for **generic ambrisentan** in combination with a phosphodiesterase type-5 (PDE-5) inhibitor [e.g. sildenafil 20 mg three times daily or tadalafil 40 mg daily]; **AND**

c. The request is for **generic ambrisentan, generic bosentan, macitentan (Opsumit), or riociguat (Adempas)**; **OR**

d. The request is for **brand ambrisentan (Letairis)**; **AND**
   i. Generic ambrisentan has been ineffective, contraindicated, or not tolerated; **OR**

e. The request is for **brand bosentan (Tracleer)**; **AND**
   i. Generic bosentan has been ineffective, contraindicated, or not tolerated; **OR**

f. The request is for **iloprost (Ventavis)** inhalation solution or **treprostinil (Tyvaso)** inhalation solution; **AND**
   i. Treatment with an endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, contraindicated, or not tolerated; **OR**

g. The request is for **treprostinil (Orenitram)** or **selexipag (Uptravi)**; **AND**
   i. Treatment with an endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, contraindicated, or not tolerated; **OR**

h. The request is for **generic treprostinil injection solution** (generic Remodulin); **OR**
      1) The request is for brand **Remodulin** and generic treprostinil injection solution has been ineffective, contraindicated, or not tolerated; **AND**
   i. Member has WHO Class IV symptoms or is classified as high risk (poor prognosis) [*see appendix table 1*]; **OR**
   ii. The member is classified as low risk (good prognosis); **AND**

2) Treatment with an ERA (e.g., bosentan, ambrisentan), AND either a PDE5 inhibitor (e.g., sildenafil, tadalafil) OR Adempas (riociguat) has been ineffective, contraindicated, or not tolerated; **OR**

iii. Member is transitioning from epoprostenol to treprostinil (Remodulin)

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)

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) 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)

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 has not been established.

IV. PH 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 a 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), and macitentan (Opsumit) 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.

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. 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. ACCF/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 do support combination therapy of PDE, ERA, and prostanoid agents.

XV. For patients with WHO functional class II or III 2019 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.

XVI. Due to the lack of head-to-head comparisons of pharmacologic agents for the treatment of PAH, and their differing burdens and risks to patients, CHEST guidelines recommend that drug therapy be chosen on the basis of a methodical evaluation of disease severity and the risk for further short-term deterioration. The optimal method of evaluation has not yet been studied; therefore, all treatment decisions should be informed by patient preferences, goals, and assessments of health-related quality of life.

CTEPH

Riociguat (Adempas) is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with persistent/recurrent 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

XVII. 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)

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

XIX. 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.

XX. 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).

VIII. Treprostinil (Tyvaso);

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.

IX. 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 trials are ongoing, and results are not yet available.

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.

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Policy Implementation/Update:

Action and Summary of Changes	Date
• 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 dosage form added • Added criteria because generic bosentan and generic ambrisentan became available we are driving patients to a more cost effective option; o Prior to getting bosentan (Tracleer), member has tried generic bosentan and treatment has been ineffective, contraindicated, or not tolerated o 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