Pulmonary arterial hypertension

MEDICAID 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 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:
  - Ambrisentan (generic, Letairis), bosentan (generic, Tracleer), and macitentan (Opsumit): Three months
  - Riociguat (Adempas), iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), 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		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 (Orenitram)	0.125 mg		90 extended-release oral tablets/30 days
	0.25 mg		
	1 mg		
	2.5 mg		
	5 mg		
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), 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); **OR**

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; **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; **OR**
        g. The request is for **treprostinil (Orenitram)** or **selexipag (Uptravi)**; **AND**
            i. Treatment with endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, 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).**

II. Ambrisentan (Letairis) is considered investigational when used for all other conditions including but not limited to:
    A. Pulmonary Hypertension Associated With Idiopathic Pulmonary Fibrosis
    B. Sarcoidosis
    C. Lowering Portal Pressure in Patients With Liver Cirrhosis
    D. Digital ulcers in systemic sclerosis

III. Bosentan (Tracleer) is considered investigational when used for all other conditions including but not limited to:
    A. Digital ulcers in systemic sclerosis

B. Raynaud phenomenon in systemic sclerosis
C. Thromboembolic pulmonary hypertension, chronic
D. Chronic obstructive pulmonary disease - Pulmonary hypertension
E. Essential hypertension

IV. Macitentan (Opsumit) is considered investigational when used for all other conditions including but not limited to:
A. Digital ulcers in systemic sclerosis
B. 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. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) 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) and idiopathic pulmonary fibrosis (IPF)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V - Sarcoidosis

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent 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. 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}.

II. 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.

III. PAH and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) are progressive and life-threatening diseases. The medication as well as the disease state need to be managed by a specialist.

IV. 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.

V. 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.

VI. 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.

VII. 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.

VIII. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), 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.

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. 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%).

XIII. 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.

XIV. 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.

Investigational Uses

I. Ambrisentan (generic, Letairis);
   A. 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.
   B. 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. But 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 and support the use.
   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. Digital ulcers 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.

   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. 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.

B. 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.

C. 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).

D. 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.

E. 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).

III. Macitentan (Opsumit);

A. 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.

B. 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, with the exception of 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).

IV. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi);

a. Pulmonary hypertension (PH) WHO Groups II-V

- Left heart disease, including congestive heart failure (CHF)
- Lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)
- Chronic thrombotic and/or embolic disease
- Sarcoidosis

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.

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. 10/19/2017
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. Taichman DB, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. CHEST 2014 Aug; 146(2):449-75.
12. CHEST website https://foundation.chestnet.org/patient-education-resources/pah/
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. 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.
15. Galie N, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl): D60-72.
16. 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
17. 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
18. 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
19. 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
20. 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
21. 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]
22. 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/...
23. Gilead Sciences. ARTEMIS-PH - Study of Ambrisentan in Subjects With Pulmonary Hypertension Associated With Idiopathic Pulmonary Fibrosis (ARTEMIS-PH). ClinicalTrials.gov Identifier: NCT00879229
24. Noorik Biopharmaceuticals AG. A Study Evaluating the Utility of Ambrisentan in Lowering Portal Pressure in Patients with Liver Cirrhosis. ClinicalTrials.gov Identifier: NCT03827200
25. Medical University of South Carolina, Gilead Sciences. Ambrisentan (Letairis) for Sarcoidosis Associated Pulmonary Hypertension. ClinicalTrials.gov Identifier: NCT00851929
26. 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
27. 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
28. Actelion. Macitentan for the Treatment of Digital Ulcers in Systemic Sclerosis Patients (DUAL-2). ClinicalTrials.gov Identifier: NCT01474122
29. 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
30. Actelion. Clinical Study on Macitentan, RT and TMZ Concurrent Therapy Followed by Maintenance Macitentan and TMZ in Newly Diagnosed Glioblastoma. ClinicalTrials.gov Identifier: NCT02254954
31. 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

32. 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.
33. 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.
34. 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.
PubMed Abstract: http://www.ncbi.nlm.nih.gov/...
PubMed Article: http://www.ncbi.nlm.nih.gov/...

Policy Implementation/Update:

	ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)	riociguat (Adempas)	Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)
Date Created	January 2013	February 2014	Prior to 3/17/2016 (no date available)
Date Effective	January 2013	March 2014	Prior to 3/17/2016 (no date available)
Last Updated	March 2014, March 2016	March 2016	03/17/2016, 3/29/2016, October 2019
Last Reviewed	03/2014, 03/2016, 12/2019	03/2016, 12/2019	03/2016, 3/2016, 12/2019
Combined	12/2019		

Action and Summary of Changes	**Date**
• 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	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)]	03/14/2016
Created [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2016