Oral Pulmonary Hypertension Agents Prior Authorization with Quantity Limit Criteria Program Summary

This program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the oral PAH Prior Authorization (PA) program is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies and according to the dosing recommended in product labeling. This program will target the oral dosage forms of these products. Brand and generic products are included in this program. The program will approve for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

TARGET AGENTS

Adcirca® (tadalafil)
Adempas® (riociguat)
Letairis® (ambrisentan)
Opsumit® (macitentan)
Orenitram® (treprostinil)
[a]Revatio® (sildenafil)
Tracleer® (bosentan)
Tyvaso® (inhaled treprostinil)
Uptravi® (selexipag)
Ventavis® (iloprost)

a – generic available, subject to prior authorization with quantity limit

Brand (generic)	GPI	Multisource Code	Quantity Per Day Limit
Adcirca (tadalafil)			
20 mg tablet	40143080000320	M, N, O, or Y	2 tablets
Adempas (riociguat)			
0.5 mg tablet	4013405000****	M, N, O, or Y	3 tablets
1 mg tablet	4013405000****	M, N, O, or Y	3 tablets
1.5 mg tablet	4013405000****	M, N, O, or Y	3 tablets
2.0 mg tablet	4013405000****	M, N, O, or Y	3 tablets
2.5 mg tablet	4013405000****	M, N, O, or Y	3 tablets
Letairis (ambrisentan)			
5 mg tablet	4016000700****	M, N, O, or Y	1 tablet
10 mg tablet	4016000700****	M, N, O, or Y	1 tablet
Opsumit (macitentan)			
10 mg tablet	4016005000****	M, N, O, or Y	1 tablet
Orenitram (treprostinil)			
0.125 mg	40170080050410	M, N, O, or Y	N/A
0.25 mg	40170080050415	M, N, O, or Y	N/A
1 mg	40170080050420	M, N, O, or Y	N/A

2.5 mg	40170080050425	M, N, O, or Y	N/A
5 mg	40170080050435	M, N, O, or Y	N/A
[a]**Revatio (sildenafil)**			
20 mg tablet	40143060100320	M, N, O, or Y	3 tablets
10 mg/mL oral suspension	40143060101920	M, N, O, or Y	2 bottles (224 mL)/30 days
Tracleer (bosentan)			
32 mg tablet	40160015007320	M, N, O, or Y	4 tablets
62.5 mg tablet	4016001500****	M, N, O, or Y	2 tablets
125 mg tablet	4016001500****	M, N, O, or Y	2 tablets
Tyvaso (inhaled treprostinil)			
0.6 mg/mL System Starter Kit (66302-206-01)	40170080002020	M, N, O, or Y	1 kit/180 days
0.6 mg/mL System Refill kit (66302-206-02)	40170080002020	M, N, O, or Y	1 package of 28 ampules/28 days
0.6 mg/mL 4 pack Carton- (66302-206-03)	40170080002020	M, N, O, or Y	7 packages of 4 ampules/28 days
Institutional starter kit (66302-206-04)	40170080002020	M, N, O, or Y	1 kit/180 days
Uptravi (selexipag)			
Titration pack	4012007000B720	M, N, O, or Y	1 pack/180 days
200 mcg tablet	40120070000310	M, N, O, or Y	2 tablets
400 mcg tablet	40120070000315	M, N, O, or Y	2 tablets
600 mcg tablet	40120070000320	M, N, O, or Y	2 tablets
800 mcg tablet	40120070000325	M, N, O, or Y	2 tablets
1000 mcg tablet	40120070000330	M, N, O, or Y	2 tablets
1200 mcg tablet	40120070000335	M, N, O, or Y	2 tablets
1400 mcg tablet	40120070000340	M, N, O, or Y	2 tablets
1600 mcg tablet	40120070000345	M, N, O, or Y	2 tablets
Ventavis (iloprost)			
10 mcg/mL	40170060002020	M, N, O, or Y	9 packages of 30 ampules/30 days
20 mcg/mL	40170060002040	M, N, O, or Y	9 packages of 30 ampules/30 days

a- generic available, subject to prior authorization with quantity limit

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Adcirca, Adempas, Letairis, Opsumit, Orenitram, Revatio, sildenafil, Tracleer, Tyvaso, Uptravi, or Ventavis will be approved when the following are met:

1. ONE of the following:
    A. ALL of the following:
        I. There is documentation that the patient is currently receiving the requested agent **OR** the prescriber states that the patient is using the requested agent AND is at risk if therapy is changed
        AND
        II. The patient has an FDA labeled indication for the requested agent
    OR

B. If Adempas, then ONE of the following:
    I. The patient has a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), WHO Group 4, as determined by a ventilation-perfusion scan and a confirmatory selective pulmonary angiography and ALL of the following:
        a. The patient has both a mean pulmonary artery pressure of ≥ 25 mmHg and a pulmonary capillary wedge pressure ≤15 mmHg
        AND
        b. ONE of the following:
            i. The patient is NOT a candidate for surgery
            OR
            ii. The patient has had a pulmonary endarterectomy AND has persistent or recurrent disease

    OR

    II. The patient has a diagnosis of pulmonary arterial hypertension (PAH), WHO Group 1 as determined by right heart catheterization and **ALL** of the following:
        a. The patient's mean pulmonary arterial pressure is ≥ 25 mmHg
        AND
        b. The patient has a pulmonary vascular resistance > 3 Wood units
        AND
        c. The patient's World Health Organization (WHO) functional class is II or greater
        AND
        d. If Adcirca, Orenitram, Revatio or sildenafil, the patient will not be taking an PDE5 inhibitor (e.g. tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra]) at the same time as the requested therapy
        AND
        e. ONE of the following:
            i. The request is for Adcirca (tadalafil) for use in combination with Letairis (ambrisentan) for dual therapy ONLY
            OR
            ii. The requested agent will be utilized as monotherapy
            OR
            iii. The requested agent will be utilized for add-on therapy to existing monotherapy (dual-therapy) [except combo requests for Adcirca with Letairis for dual therapy], and ALL of following:
                1. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy
                AND
                2. The requested agent is in a different therapeutic class

            OR
            iv. The requested agent will be utilized for add-on therapy to existing dual therapy (triple therapy) and ALL of the following:
                1. The patient is WHO functional class III or IV
                AND

2. A prostanoid has been started as one of the agents in the triple therapy unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a prostanoid
AND
3. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy
AND
4. All three agents in the triple therapy are from a different therapeutic class

OR

III. The patient has another FDA labeled diagnosis for the requested agent

OR

C. If Adcirca, Letairis, Opsumit, Orenitram, Revatio, sildenafil, Tracleer, Tyvaso, Uptravi, or Ventavis, then patient has a diagnosis of pulmonary arterial hypertension (PAH), WHO Group 1 as determined by right heart catheterization and **ALL** of the following:
   I. The patient's mean pulmonary arterial pressure is ≥ 25 mmHg
   AND
   II. The patient has a pulmonary vascular resistance > 3 Wood units
   AND
   III. The patient's World Health Organization (WHO) functional class is II or greater
   AND
   IV. If Adcirca, Orenitram, Revatio or sildenafil, the patient will not be taking another PDE5 inhibitor (e.g. tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra]) at the same time as the requested therapy
   AND
   V. ONE of the following:
      a. The request is for Adcirca (tadalafil) for use in combination with Letairis (ambrisentan) for dual therapy ONLY
      OR
      b. The requested agent will be utilized as monotherapy
      OR
      c. The requested agent will be utilized for add-on therapy to existing monotherapy (dual-therapy) [except combo requests for Adcirca with Letairis for dual therapy], and ALL of following:
         i. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy
         AND
         ii. The requested agent is in a different therapeutic class
      OR
      d. The requested agent will be utilized for add-on therapy to existing dual therapy (triple therapy) and ALL of the following:
         i. The patient is WHO functional class III or IV
         AND
         ii. A prostanoid has been started as one of the agents in the triple therapy unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a prostanoid
         AND

iii. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy
AND
iv. All three agents in the triple therapy are from a different therapeutic class

AND

VI. If the request is for the brand Adcirca (not applicable to requests for Adcirca + Letairis for dual therapy) or Revatio then ONE of the following:
a. The patient's medication history includes use of a generic prerequisite agent (e.g. sildenafil)
OR
b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a generic prerequisite agent (e.g. sildenafil)
OR
c. The prescriber has submitted documentation in support of the requested therapeutic use of the requested brand agent which has been reviewed and approved by the Clinical Review pharmacist

OR

D. The patient has another FDA approved diagnosis for the requested agent

AND

2. The patient does not have any FDA labeled contraindications to therapy with the requested agent

AND

3. For all agents except Orenitram, ONE of the following:
A. The requested quantity (dose) is NOT greater than the program quantity limit
OR
B. ALL of the following:
I. The requested quantity (dose) is greater than the program quantity limit
AND
II. The requested quantity (dose) is less than or equal to the FDA labeled dose
AND
III. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

OR

C. ALL of the following:
I. The requested quantity (dose) is greater than the program quantity limit
AND
II. The requested quantity (dose) is greater than the FDA labeled dose
AND
III. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

Renewal Evaluation
Adcirca, Adempas, Letairis, Opsumit, Orenitram, Revatio, sildenafil, Tracleer, Uptravi, Tyvaso or Ventavis will be approved for renewal when the following met:

1. The patient has been previously approved for therapy through Prime Therapeutics PA process
   AND
2. The patient is responding to therapy
   AND
3. The patient does not have any FDA labeled contraindications to therapy with the requested agent
   AND
4. For all agents except Orenitram, ONE of the following:
   - A. The requested quantity (dose) is NOT greater than the program quantity limit
     OR
   - B. ALL of the following:
     - I. The requested quantity (dose) is greater than the program quantity limit
       AND
     - II. The requested quantity (dose) is less than or equal to the FDA labeled dose
       AND
     - III. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

     OR
   - C. ALL of the following:
     - I. The requested quantity (dose) is greater than the program quantity limit
       AND
     - II. The requested quantity (dose) is greater than the FDA labeled dose
       AND
     - III. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATIONS AND DOSAGE[1,2,15-17,21,25,27-29]

Available Products	Indication	Dosage and Administration
Adcirca (tadalafil)	Treatment of pulmonary arterial hypertension (*WHO Group I) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).	40 mg (two 20 mg tablets) orally once daily; dividing the dose over the course of the day is not recommended
Adempas (riociguat)	Riociguat is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (*WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class. Riociguat is also indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (*WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy was shown in patients on monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).	1 mg orally three times daily. Initial doses may be started at 0.5 mg three times daily for those who may not tolerate the hypotensive effects. Up-titrate the dose by 0.5 mg three times daily according to blood pressure up to a maximum dose of 2.5 mg three times daily. Dose increases should be no sooner than 2 weeks apart.
Letairis (ambrisentan)	Treatment of pulmonary arterial hypertension (*WHO Group 1): •To improve exercise capacity and delay clinical worsening. •In combination with tadalafil to reduce the risks of disease	5 mg orally once daily, with or without tadalafil 20mg once daily; At 4-week intervals, either the dose of Letairis or tadalafil can be increased, as needed and tolerated, to Letairis 10mg or tadalafil 40 mg.

Available Products	Indication	Dosage and Administration
	progression and hospitalization for worsening PAH, and to improve exercise ability. • Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).	
Opsumit (macitentan)	Treatment of pulmonary arterial hypertension (*WHO Group 1) to delay disease progression (inclusive of death, initiation of prostanoids, or clinical worsening) of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). It also reduced hospitalization for PAH. 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 were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).	10 mg orally once daily. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended.
Orenitram (treprostinil)	Treatment of pulmonary arterial hypertension (*WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with	Starting dose is 0.25 mg orally twice daily 12 hours apart or 0.125 mg three times daily taken approximately 8 hours apart. Titrate by 0.25 or 0.5 mg twice daily or 0.125 mg three times daily, not more than every 3-4 days as tolerated. Max dose based on tolerability.

Available Products	Indication	Dosage and Administration
	connective tissue disease (19%). When used as the sole vasodilator, the effect of 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.	
Revatio (sildenafil citrate)	Treatment of pulmonary arterial hypertension (*WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD)(25%). Limitation of use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.	**Oral tablets:** 5 mg or 20 mg orally three times daily 4-6 hours apart; no greater efficacy seen with higher doses in clinical trial **IV bolus injection:** 2.5 mg or 10 mg three times daily; IV injection is for patients temporarily unable to take oral medication **Powder for oral suspension:** 5 mg or 20 mg orally three times daily 4-6 hours apart
Tracleer (bosentan)	Treatment of pulmonary arterial hypertension (*WHO Group I): • in adults to improve exercise ability and to decrease clinical worsening. Studies 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	Patients >12 y.o. and >40 kg: 62.5 mg orally twice daily for 4 weeks, and then increase to 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of hepatotoxicity. Patients >12 y.o. and <40 kg:: Initial and maintenance dose is 62.5 mg orally twice daily Patients ≤12 years of age and ≥4-8 kg: 16 mg orally twice daily for both initial and maintenance dose >8-16 kg: 32 mg orally twice daily for both initial and maintenance dose

Available Products	Indication	Dosage and Administration
	congenital heart disease with left-to-right shunts (18%). • in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.	>16-24 kg: 48 mg orally twice daily for both initial and maintenance dose >24-40 kg: 64 mg orally twice daily for both initial and maintenance dose
Tyvaso (inhaled treprostinil)	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on background of bosentan (an endothelin receptor antagonist) or sildenafil (a PDE 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.	• Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours. • Initial dosage: 3 breaths [18 mcg] orally per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths. • Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated. • Titrate to target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated.
Uptravi (selexipag)	Treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness 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%), PAH	• Starting dose: 200 mcg orally twice daily. • Increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily. Maintenance dose is determined by tolerability

Available Products	Indication	Dosage and Administration
	associated with congenital heart disease with repaired shunts (10%).	
Ventavis (iloprost)	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).	The first inhaled dose should be 2.5 mcg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 mcg and maintained at that dose; otherwise maintain the dose at 2.5 mcg. Ventavis should be taken 6 to 9 times per day (no more than once every 2 hours) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mcg (5 mcg 9 times per day).

* – WHO = World Health Organization

CLINICAL RATIONALE

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries, characterized by vascular narrowing leading to a progressive increase in pulmonary vascular resistance. Vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis contribute to the increased pulmonary vascular resistance in PAH.[3] The most common presenting symptom is exertional dyspnea. Therapy includes drugs for anticoagulation, for decreasing pulmonary vascular resistance, for underlying disease, and for right ventricular failure. Vasodilators that have been found effective include calcium channel blockers (e.g., high dose diltiazem, nifedipine), and prostacyclin (e.g., epoprostenol, treprostinil). Endothelin receptor antagonists (ERA) and phosphodiesterase type 5 (PDE-5) inhibitors have been shown to increase exercise tolerance.[26]

To date, the majority of FDA approved drug therapies (vasodilators, calcium channel blockers, prostanoids, and endothelin receptor antagonists) are designed to treat patients in Group 1 which includes subtypes of idiopathic, heritable, and those associated with other diseases (e.g. connective tissue disorders, HIV, or congenital heart disease). However, Group 4 is addressed as well, which is due to chronic thrombotic and/or embolic disease including chronic thromboembolic pulmonary hypertension (CTEPH). Ventilation/perfusion scan planar images combined with a confirmatory CT pulmonary angiography remain the preferred diagnostic tests for CTEPH despite advances in computed tomography (CT) and magnetic resonance (MR). CT and MR can be used in conjunction with the preferred diagnostic tests to identify complications of the disease, but should not be solely relied upon due to concerns of false-positive cases mimicking CTEPH. CTEPH is defined as mean pulmonary arterial pressure ≥25mmHg and pulmonary capillary wedge pressure ≤15 mmHg in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least 3 months of effective anticoagulation.[32-34] CTEPH is traditionally treated with surgery. Pulmonary endarterectomy is the treatment of choice and the only potential for cure for symptomatic, operable, CTEPH patients.[22] Surgery however, is not an option for all patients and some patients who have undergone surgery have persistent or recurrent pulmonary hypertension.[23]

Treatment Guidelines

The 5th World Symposium on Pulmonary Hypertension evidence-based treatment algorithm:[11]

- Head-to-head comparisons among different compounds are not available, no evidence-based first line treatment can be proposed for either WHO-FC II or III patients.
- WHO-FC II: Either an ERA (it is noted that macitentan has morbidity and mortality as the primary endpoint in RCT; however, they do not prefer one over the other), a PDE5 inhibitor, or riociguat.
- WHO-FC III: Any of the following can be used – An ERA, A PDE5 inhibitor, epoprostenol, iloprost (inhaled), riociguat, or treprostinil subcutaneous or inhaled (it is noted that epoprostenol IV and macitentan have morbidity and mortality as primary endpoint in RCT or reduction in all-cause mortality (prospectively defined); however, none are preferred over the other.
- WHO- FC IV: Epoprostenol improves symptoms, exercise capacity, and hemodynamics in both clinical conditions, and is the only treatment shown to reduce mortality in idiopathic PAH in a RCT. Continuous IV epoprostenol is recommended as first-line therapy for WHO-FC IV PAH patients because of the survival benefit in this subset. In absence of IV epoprostenol all other compounds may be utilized. In these patients initial combination therapy may also be considered.
- In case of inadequate clinical response, sequential combination therapy should be considered. Combination therapy can either include an ERA + PDE5 inhibitor or a prostanoid plus and ERA or a prostanoid plus a PDE5 inhibitor. Riociguat can be considered as a potential alternative to PDE inhibitor in the different types of double combinations. The combination of riociguat and PDE5 inhibitors is contraindicated.
- In case of inadequate clinical response with double combination therapy, triple combination therapy should be attempted.

The American College of Chest Physicians (CHEST) guidelines (2014) state[26]:

- WHO FC II [treatment naïve and not a candidate for or failure to calcium channel blocker (CCB) therapy]: monotherapy with an endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE5) inhibitor, or riociguat
- WHO FC III [treatment naïve and not a candidate for or failure to calcium channel blocker (CCB) therapy]: monotherapy with an ETRA, a PDE5 inhibitor, or riociguat
- WHO FC III treatment naïve with evidence of rapid progression of their disease, or other markers of a poor clinical prognosis: initial treatment with a parenteral prostanoid.
- WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents: addition of a parenteral or inhaled prostanoid.
- WHO FC IV treatment naïve: monotherapy with a parenteral prostanoid agent.
- WHO FC III or IV with unacceptable or deteriorating clinical status despite established PAH pharmacotherapy, a third class of PAH therapy should be started

World Health Organization Functional Classification of Patients with Pulmonary Hypertension[26]

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart

The 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of pulmonary hypertension state that if a patient is vasoreactive, a CCB should be given as first line. Non-responders to acute vasoreactivity testing can be treated with either initial monotherapy or combination therapy. The choice of drug depends on approval status, labeling, route of administration, side-effect profile, potential interaction with background therapies, patient preference, co-morbidities, physician experience and cost. Since a head-to-head comparison between initial combination therapy with ambrisentan plus tadalafil has proven superior to initial monotherapy with either agent alone in delaying clinical failure, a higher grade of recommendation has been given to this initial combination. In non-vasoreactive and treatment-naive patients at high risk, initial combination therapy including IV prostacyclin analogues should be considered. IV epoprostenol should be prioritized since it has reduced the 3-month rate of mortality in high-risk PAH patients. In case of inadequate clinical response with sequential double combination therapy, triple combination therapy should be attempted.[30,31]

The Chest guidelines recognize that there is still a lack of head-to-head comparisons of pharmacologic agents for the treatment of PAH, and because of their differing burdens and risks to patients, it is recommended 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 been studied. No one agent can be definitively recommended preferentially.

Additionally, it notes that adding a second class of PAH therapy for patients whose clinical status remains unacceptable despite established PAH-specific monotherapy requires that the clinician assess whether the patient has received an adequate trial of the initial monotherapy. At present, this assessment combines evaluation of the duration of monotherapy, the expected response to the monotherapy, the observed response to the monotherapy, and the patient's severity of illness and pace of decline. Unacceptable clinical status will vary for individual patients and clinicians, but symptomatic limitation of desired physical activities usually guide these decisions.

For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, the guideline advises an addition of a second class of PAH therapy to improve exercise capacity. Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH. Data from RCTs are not available to inform the addition of a third pharmacologic class of PAH medication. However, addition of a third class of PAH medication usually indicates poor functional status. In this setting, the guidelines state that treatment with a parenteral prostanoid therapy must be considered.

The recommendations for combination therapy should be used as general guidelines until more is known about which combinations are most efficacious and the optimal timing of combining therapies is available. Until then, an individualized approach should be used by a practitioner who has experience using combination therapy for PAH. In general, escalation of therapy and referral for lung transplantation evaluation should occur when a patient has evidence of disease progression on combination therapy.[26]

REFERENCES

1. Revatio prescribing information. Pfizer. April 2015.
2. Adcirca prescribing information. Eli Lilly and Company. April 2015.

3. Humbert M, Morrell NW, Archer SL, et al. Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2004;43:13S-24S.
4. Deleted.
5. Deleted in current version. See reference 11.
6. See Reference 26.
7-10. Deleted.
11. 5th World Symposium on PAH. *J Am Coll Cardiol.* 2013;62 (25):D61-D72.
12-14. Deleted.
15. Letairis prescribing information. Gilead. October 2015.
16. Tracleer prescribing information. Actelion. September 2017.
17. Opsumit prescribing information. Actelion Pharmaceuticals, Inc. South San Francisco, CA. October 2016.
18-20. Deleted.
21. Adempas prescribing information. Bayer HealthCare. February 2017.
22. Bayer Healthcare FDA Advisory Committee Briefing Document. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm357806.htm. Accessed 3/16/17.
23. Hossein-Ardeschir G, D-Armini AM, Grimminger F et al. Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension. *N Engl J Med* 2013;369:319-29.
24. Deleted.
25. Orenitram prescribing information. United Therapeutics Corporation. Research Triangle Park, NC. January 2017.
26. Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline and Expert Panel Report. *Chest.* 2014;146(2):449-475. doi:10.1378/chest.14-0793. http://journal.publications.chestnet.org/article.aspx?articleid=1881654. Accessed 3/16/2017.
27. Tyvaso Prescribing Information. United Therapeutics Corp. June 2016.
28. Ventavis Prescribing Information. Actelion. November 2013
29. Uptravi Prescribing Information. Actelion. December 2015.
30. N Engl J Med. 2015 Aug 27;373(9):834-44. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension.
31. 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH. Accessed 3/16/2017 http://eurheartj.oxfordjournals.org/content/early/2015/08/28/eurheartj.ehv317#T23
32. Irene Lang, MD and Michael Madani, MD. Contemporary Reviews in Cardiovascular Medicine: Update on Chronic Thromboembolic Pulmonary Hypertension. Circulation. 2014;130:508-518.
33. Nick Kim, MD. Chronic Thomboembolic Pulmonary Hypertension: Diagnosis. Medscape Pharmacists. http://www.medscape.org/viewarticle/556058_3. Accessed on 3/16/2017.