Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

Therapeutic Class

- **Overview/Summary:** The oral pulmonary hypertension agents are Food and Drug Administration (FDA)-approved for the treatment of patients with World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH); however, there are differences in the study populations for which their FDA-approvals were based.[1-10] Typically, PAH is characterized by an elevated pulmonary arterial pressure and an increased pulmonary vascular resistance leading to right-sided heart failure. The prevalence of PAH is estimated to be 15 cases/million adults. The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy.[11] The WHO classifies pulmonary hypertension into five groups. WHO Group I encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorders, portal hypertension, human immunodeficiency virus infection, drugs and toxins and other disorders that affect the small pulmonary muscular arterioles. Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.[12] Five classes of medications are currently FDA-approved for the treatment of WHO Group I PAH: prostacyclin analogues (prostanoids), prostacyclin receptor agonists, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[1-10,13] In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation.[11] The prostanoids act as vasodilators and platelet aggregation inhibitors. Iloprost (Ventavis®), treprostinil (Tyvaso®) and treprostinil diolamine (Orenitram®) are the only prostanoids currently available orally; however, other products are available for intravenous or subcutaneous administration.[1-3] Selexipag (Uptravi®) is a prostacyclin receptor agonist, which acts via the same receptor as the prostanoids, but is structurally distinct from prostacyclin.[4] Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B.[5-7,11] Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance.[5,6] The ERAs, ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) competitively bind to both receptors with different affinities. Ambrisentan is highly selective for the ET_A receptor, while bosentan is slightly more selective for the ET_A receptor than the ET_B receptor. Macitentan is associated with a high affinity and sustained occupancy of both ET receptors. However, the clinical significance of receptor affinities of the ERAs has not been established.[5-7] In patients with PAH there is also an impaired release of nitric oxide by the vascular endothelium thereby reducing cyclic guanosine monophosphate (cGMP) concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.[11] The PDE-5 inhibitors, sildenafil (Revatio®) and tadalafil (Adcirca®), increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.[8,9] Soluble guanylate cyclase (sGC) is an enzyme present in the cardiopulmonary system and is the receptor for nitric oxide. When bound to nitric oxide, sGC catalyzes synthesis of cGMP, which plays a role in the regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Riociguat (Adempas®) stimulation of this nitric oxide-sGC-cGMP pathway leads to increased generation of cGMP and thus, vasodilation.[10]

Table 1. Current Medications Available in Therapeutic Class[1-9,12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Ambrisentan (Letairis®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.*	Tablet: 5 mg 10 mg	-
Bosentan (Tracleer®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.†	Tablet: 62.5 mg 125 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Iloprost (Ventavis®)	Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration.‡	Ampule for inhalation: 10 µg/mL 20 µg/mL	-
Macitentan (Opsumit®)	Treatment of PAH (WHO Group I) to delay disease progression.‖#	Tablet: 10 mg	-
Riociguat (Adempas®)	Treatment of PAH (WHO Group I) to improve exercise ability, improve WHO functional class and delay clinical worsening and treatment of persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity.‖	Tablet: 0.5 mg 1 mg 1.5 mg 2 mg 2.5 mg	-
Selexipag (Uptravi®, Uptravi Titration Pack®)	Treatment of PAH (WHO Group I) in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH and to improve exercise ability‡‡		
Sildenafil (Revatio®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.§‖	Tablet: 20 mg Vial for injection: 0.8 mg/mL Powder for oral suspension: 10 mg/mL	✔
Tadalafil (Adcirca®)	Treatment of PAH (WHO Group I) to improve exercise ability.¶	Tablet: 20 mg	-
Treprostinil (Tyvaso®)	Treatment of PAH (WHO Group I) to improve exercise ability. **	Ampule for inhalation: 0.6 mg/mL	-
Treprostinil (Orenitram®)	Treatment of PAH (WHO Group I) to improve exercise ability.††	Extended-release tablet: 0.125 mg 0.25 mg 1 mg 2.5 mg	-

CTEPH=Chronic Thromboembolic Pulmonary Hypertension, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization

*Studies establishing effectiveness included predominantly patients with World Health Organization (WHO) Functional Class II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64%) or PAH associated with connective tissue diseases (32%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies establishing effectiveness included predominately patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%), PAH associated with connective tissue diseases (23%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

‖ Approved for use in adults only.

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

#Disease progression included death, initiation of intravenous or subcutaneous prostanoids or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).

** Studies included predominantly patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

††Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue diseases (19%).
‡‡ Studies included predominantly patients with NYHA class II or III symptoms and etiologies of idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%)

Evidence-based Medicine

- Randomized controlled trials have demonstrated the efficacy of the oral pulmonary arterial hypertension agents in increasing exercise capacity and improving World Health Organization and New York Heart Association functional class; however, no head to head trials have been conducted.[16-47]
- Only small studies evaluating the effect of combination therapy have been conducted, and statistically significant improvements have not consistently been demonstrated.[11,23,35,346,41, 43,45]
- Common adverse events in the prostanoids class are jaw pain, diarrhea, headache and flushing.[13] Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests. [13] The phosphodiesterase-5 inhibitors are generally well tolerated and common adverse effects include headache, flushing, and dyspepsia.[13] The most common adverse events associated with the soluble guanylate cyclase stimulators can be ascribed to the vasodilatory mechanism of action, including headache, dizziness, nausea and hypotension.[9]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Oral calcium-channel blockers (CCB) are recommended only for patients with positive acute vasodilator response to testing.[11,14,15]
    - Oral therapy with either a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist or riociguat is recommended as first-line treatment in patients who are considered lower risk and are not candidates for CCBs.[11,14,15]
    - Use of inhaled or parenteral prostanoids should not be chosen as initial therapy for treatment naïve PAH patients with WHO functional class II symptoms or as second line agents for PAH patients with WHO functional class II symptoms who have not met their treatment goals.[14]
    - For WHO class III patients, addition of a parenteral or inhaled prostanoid to mono- or dual-oral therapy is recommended if rapid progression occurs, or there is poor clinical prognosis.[11,14]
    - Intravenous prostanoids are the preferred treatment in patients at higher risk and poor prognostic indexes.[11,14]
    - If a patient cannot or does not wish to use intravenous medications, they may use inhaled prostanoids and an endothelin receptor antagonist for higher risk or poorer prognostic indexes.[14]
    - Combining therapies with different mechanisms of action, either in sequential pattern or simultaneously at the beginning of treatment for the management of PAH is recommended.

- Other Key Facts:
    - Ambrisentan, bosentan, macitentan and riociguat are distributed through a restricted distribution program.[2,3,8,9]
    - Sildenafil tablet is the only oral pulmonary arterial hypertension agent that is available generically.
    - In August 2012, the prescribing information for sildenafil was updated to include a warning against the use of sildenafil in pediatric patients. This was due to increased mortality seen in long-term clinical trials that included pediatric patients.[6]

References

1. Ventavis® [package insert]. South San Francisco (CA): Actelion Pharmaceuticals, Inc.; 2013 Nov.
2. Tyvaso® [package insert]. Research Triangle Park (NC): United Therapeutics Corp.; 2014 Aug.
3. Orenitram® [package insert]. Research Triangle Park (NC): United Therapeutics Corp; 2016 Feb.
4. Uptravi® and Uptravi Titration Pack® [package insert]. South San Francisco (CA): Actelion Pharmaceuticals US, Inc.; 2015 Dec.
5. Letairis® [package insert]. Foster City (CA): Gilead Sciences Inc.; 2015 Oct.
6. Tracleer® [package insert]. South San Francisco (CA): Actelion Pharmaceuticals US, Inc.; 2015 Dec.
7. Opsumit® [package insert]. San Francisco (CA): Actelion Pharmaceuticals US, Inc.; 2016 Feb.

8. Revatio® [package insert]. New York (NY): Pfizer Inc.; 2014 Mar.
9. Adcirca® [package insert]. Indianapolis (IN): Eli Lilly and Company; 2014 April.
10. Adempas® [package insert]. Whippany (NJ): Bayer HealthCare Pharmaceuticals Inc.; 2014 Aug.
11. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation. 2009 Apr 28;119(16):2250-94.
12. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009 Jun 30;54(1 Suppl):S43-54.
13. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [Accessed 2015 Jan 12]. Available from: http://www.thomsonhc.com/.
14. Taichman DB, Ornelas J, Chung L, Klinger J et al. Pharmacological Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline. Chest. 2014 July. Published online http://journal.publications.chestnet.org/
15. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European Heart Journal. Aug 29 2015.
16. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, et al. Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. 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. 2008 Jun 10;117(23):3010-9.
17. Badesch DB, Feldman J, Keogh A, Mathier MA, Oudiz RJ, Shapiro S, et al. ARIES-3: ambrisentan therapy in a diverse population of patients with pulmonary hypertension. Cardiovasc Ther. 2012 Apr;30(2):93-9.
18. Oudiz RJ, Galiè N, Olschewski H, Torres F, Frost A, Ghofrani HA, et al. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009 Nov 17;54(21):1971-81.
19. Fox B, Langleben D, Hirsch AM, Schlesinger RD, Eisenberg MJ, Joyal D, et al. Hemodynamic Stability After Transitioning Between Endothelin Receptor Antagonists in Patients With Pulmonary Arterial Hypertension. Can J Cardiol. 2012 Jul 20. [Epub ahead of print]
20. Yoshida S, Shirato K, Shimamura R, Iwase T, Aoyagi N, Nakajima H. Long-term safety and efficacy of ambrisentan in Japanese adults with pulmonary arterial hypertension. Curr Med Res Opin. 2012 Jun;28(6):1069-76.
21. Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. Lancet. 2001 Oct 6;358(9288):1119-23.
22. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002 Mar 21;346(12):896-903.
23. McLaughlin VV, Oudiz RJ, Frost A, Tapson VF, Murali S, Channick RN, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2006 Dec 1;174(11):1257-63.
24. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ, et al. Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002 Aug 1;347(5):322-9.
25. Galie N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer G, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet. 2008 Jun 21;371(9630):2093-100.
26. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013 Aug 29;369(9):809-18.
27. Channick RN, Delcroix M, Galie N, Ghofrani HA, Hunsche E, Jansa P, et al. Macitentan Reduces Pah-Related Hospitalizations: Results From The Randomized Controlled Seraphin Trial. American Journal of Respiratory and Critical Care Medicine [abstract]. 2013 May 20;187:A3527.
28. Mehta S, Channick RN, Delcroix M, Galie N, Ghofrani HA, Hunsche E, et al. Macitentan Improves Health-Related Quality of Life in Pulmonary Arterial Hypertension: Results from The Randomized Controlled Seraphin Trial. American Journal of Respiratory and Respiratory and Critical Care Medicine [abstract]. 2013 May 20;187:A3269.
29. Ghofrani HA, D'Armini AM, Grimminger FG, Hoeper MM, Jansa P, Kim NH et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. NEJM. 2013 Jul; 369(4):319-29.
30. Ghofrani HA, Galie N, Grimminger F, Grunig E, Humbert M, Jing ZC. Riociguat for the Treatment of pulmonary arterial hypertension. NEJM. 2013 Jul; 369(4):330-40.
31. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. New England Journal of Medicine. 2015;373(26):2522-2533.
32. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005 Nov 17;353(20):2148-57.
33. Rubin LJ, Badesch DB, Fleming TR, Galiè N, Simonneau G, Ghofrani HA, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. Chest. 2011 Nov;140(5):1274-83.
34. Simonneau G, Rubin LJ, Galiè N, Barst RJ, Fleming TR, Frost AE, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. Ann Intern Med. 2008 Oct 21;149(8):521-30.
35. Yanagisawa R, Kataoka M, Taguchi H, Kawakami T, Tamura Y, Fukuda K, et al. Impact of first-line sildenafil mono treatment for pulmonary arterial hypertension. Circ J. 2012 Apr 25;76(5):1245-52.

36. Galie N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, et al. Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009 Jun 9;119(22):2894-903.
37. Oudiz RJ, Brundage BH, Galiè N, Ghofrani HA, Simonneau G, Botros FT, et al. Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study. J Am Coll Cardiol. 2012 Aug 21;60(8):768-74.
38. Barst RJ, Oudiz RJ, Beardsworth A, Brundage BH, Simonneau G, Ghofrani HA, et al. Tadalafil monotherapy and as add-on to background bosentan in patients with pulmonary arterial hypertension. J Heart Lung Transplant. 2011 Jun;30(6):632-43.
39. Jing ZC, Parikh K, Pulido T, Jerjes-Sanchew C, White J, Allen R et al. FREEDOM-M: Efficacy and safety of oral treprostinil diethanolamine as monotherapy in patients with pulmonary arterial hypertension. Circulation. 2013 Jan;127:624-33.
40. Tapson VF, Torres F, Kermeen F, Keogh AM, Allen RP, Frantz RP, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study). Chest. 2012;142(6):1383-90.
41. Tapson VF, Jing ZC, Xu, KF, Pan L, Feldman J, Kiely DG, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study). Chest. 2013;144(3):952-8.
42. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol. 2010 May 4;55(18):1915-22.
43. Benza RL, Seeger W, McLaughlin VV, Channick RN, Voswinckel R, Tapson VF, et al. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) study open-label extension. J Heart Lung Transplant. 2011 Dec;30(12):1327-33.
44. Perez VA, Rosenzweig E, Rubin LJ, Poch D, Bajwa A, Park M, et al. Safety and Efficacy of Transition from Systemic Prostanoids to Inhaled Treprostinil in Pulmonary Arterial Hypertension. Am J Cardiol. 2012 Nov 15;110(10):1546-50.
45. Benza RL, Rayburn BK, Tallaj JA, Pamboukian SV, Bourge RC. Treprostinil-based therapy in the treatment of moderate-to-severe pulmonary arterial hypertension: long-term efficacy and combination with bosentan. Chest. 2008 Jul;134(1):139-45.
46. Urbanowicz T, Straburzyńska-Migaj E, Katyńska I, Araszkiewicz A, Oko-Sarnowska Z, Grajek S, et al. Sustained improvement of clinical status and pulmonary hypertension in patients with severe heart failure treated with sildenafil. Ann Transplant. 2014 Jul 9;19:325-30. doi: 10.12659/AOT.890657.
47. Corte TJ, Keir GJ, Dimopoulos K, Howard L, Corris PA, Parfitt L, et al. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. Am J Respir Crit Care Med. 2014 Jul 15;190(2):208-17. doi: 10.1164/rccm.201403-0446OC.