RX.PA.029.MPC Pulmonary Arterial Hypertension (PAH) Products

The purpose of this policy is to define the prior authorization process for pulmonary arterial hypertension products.

DEFINITIONS

Chronic thromboembolic pulmonary hypertension (CTEPH) – a mean pulmonary artery pressure greater than 25 mm Hg that persists 6 months after pulmonary embolism is diagnosed.

Pulmonary arterial hypertension (PAH) – PAH is a syndrome resulting from restricted flow through the pulmonary arterial circulation resulting in increased pulmonary vascular resistance and subsequent right heart failure. The diagnosis of PAH requires confirmation with a complete right heart catheterization. The hemodynamic definition of PAH includes a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg in the setting of a normal pulmonary capillary wedge pressure (PCWP) of 15 mm Hg or less with a pulmonary vascular resistance (PVR) greater than 3 Wood units.

Pulmonary endarterectomy (PEA) – surgical procedure to remove obstructive hardened, thromboembolic materials from the pulmonary arteries to improve hemodynamics in patients CTEPH.

Pulmonary Hypertension Specialist – a cardiologist or pulmonologist who is a member of the Pulmonary Hypertension Association

Pulmonary Vascular Resistance (PVR) – PVR (wood units) = (mPAP – PCWP)/ Cardiac Output. PVR (wood units) = PVR (dynes-sec-cm-5)/80

WHO Etiologic Classification of Pulmonary Hypertension

Group 1	Pulmonary arterial hypertension
Group 2	Pulmonary hypertension with left heart disease
Group 3	Pulmonary hypertension associated with lung disease and/or hypoxemia
Group 4	Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Group 5	Miscellaneous

WHO Functional Classification of Pulmonary Hypertension

Class I	Members with no symptoms and for whom ordinary physical activity does not cause dyspnea or fatigue, chest pain or near syncope.

Class II	Members who are comfortable at rest but who have symptoms** with ordinary physical activity.
Class III	Members who are comfortable at rest but have symptoms** with less-than-ordinary effort.
Class IV	Members who have symptoms** at rest

**Key symptoms of PH include dyspnea or fatigue, chest pain, or near syncope (fainting)

PREFERRED – PA REQUIRED	NON-PREFERRED – PA REQUIRED
Phosphodiesterase-5 (PDE-5) Inhibitors	
Adcirca (tadalafil) tablets [Functional class II, III, or IV]	Revatio (sildenafil)- tablets, oral susp [Functional class II, III, or IV]
Sildenafil (generic for Revatio) tablets [Functional class II, III, or IV]	
Prostacyclin Analogs	
Epoprostenol (generic for Flolan) [Functional class III or IV]	Orenitram (treprostinil) [Functional class II or III]
Remodulin (treprostinil) [Functional class II, III, or IV]	Uptravi (selexipag) [Functional class II or III]
Tyvaso (treprostinil) [Functional class III]	Flolan (epoprostenol) [Functional class III or IV]
Epoprostenol (generic for Veletri) [Functional class III or IV]	Veletri (epoprostenol) [Functional class III or IV]
Ventavis (iloprost) inh soln [Functional class III or IV]	
Endothelial-Receptor Antagonists	
Letairis (ambrisentan) tablets [Functional class II, III, or IV]	
Opsumit (macitentan) tablets [Functional class II or III]	
Tracleer (bosentan) tablets [Functional class II, III, or IV]	
Soluble Guanylate Cyclase Stimulators	
Adempas (riociguat) tablets [Functional class II or III]	

PROCEDURE

A. Initial Authorization Criteria:

Must meet all of the criteria listed under the respective diagnosis:

1. Pulmonary Arterial Hypertension (PAH):

- Patient must be age 18 years or older
- Must have a diagnosis of PAH classified as WHO Group 1
- Must be prescribed by or in consultation with a cardiologist of pulmonologist experienced in the diagnosis and treatment of PAH
- Documentation of baseline 6-minute walk test
- Documentation of right catheterization with mean pulmonary artery pressure (mPAP) > 25 mmHg

- Must not be used concomitantly with organic nitrates (e.g., isosorbide mononitrate, isosorbide dinitrate, nitroglycerin)
- Must have appropriate New York Heart Association (NYHA) or WHO functional class symptoms for the requested drug listed in the table above
- For combination therapy (2+ PAH agents)
    - Remodulin (treprostinil) and Flolan (epoprostenol) combination is allowed in patients who require transition from Flolan. Combination therapy for the down-titration of Flolan can be up to 14 days.
    - Adempas must NOT be used in combination with PDE-5 inhibitors [e.g., Adcirca (tadalafil), Revatio (sildenafil), sildenafil (generic for Revatio)]
    - Must have documentation of an inadequate clinical response to monotherapy, defined as:
        - For WHO Functional Assessment Classification II or III: Resulting clinical status defined as stable and not satisfactory, or unstable and deteriorating
        - For WHO Functional Assessment Classification IV: No rapid improvement to WHO Functional Assessment Classification III or better
        - Clinical status defined as stable and not satisfactory
- For Tracleer in members less than 18 years of:
    - Must be age 3 years or older
    - Must have idiopathic or congenital PAH WHO Group 1
    - Must provide baseline pulmonary vascular resistance (PVR)
- For non-preferred agents:
    - Must have a documented trial and failure, contraindication, or intolerance to at least TWO of the preferred agents within the same class
- For Letairis, Opsumit, Adempas, and Tracleer verification prescriber and patient are enrolled in associated REMS Program
- If patient is a woman of childbearing potential, documented contraceptive plan and negative pregnancy test

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH): Adempas only

- Requested drug must be a soluble guanylate cyclase stimulator (Adempas)
- Must be age 18 years or older
- Must be prescribed by or in consultation with a cardiologist of pulmonologist experienced in the diagnosis and treatment of PAH
- Must have a diagnosis of CTEPH classified as WHO Group 4
- Must have New York Heart Association (NYHA) or WHO functional class II or III symptoms

- Documentation of baseline 6-minute walk test
- Documentation of Pulmonary vascular resistance (PVR) > 3 Wood units following pulmonary thromboendarterectomy
- Documentation of ALL of the following:
  - Patient inoperable for pulmonary endarterectomy
  - PVR >3 Wood units
  - Mean pulmonary artery pressure (mPAP) >25 mmHg
- Must not be used concomitantly with organic nitrates or phosphodiesterase-5 inhibitors [Revatio (sildenafil) or Adcirca (tadalafil)]
- Verification prescriber and patient are enrolled in Adempas REMS Program
- If patient is a woman of childbearing potential, documented contraceptive plan and negative pregnancy test

Note: Documentation MUST include either paid claims OR specific dates of use for medication trials AND/OR chart documentation from the provider noting a contraindication, intolerance, or failure to all pre-requisite medications

B. Must be prescribed at a dose within the manufacturer's dosing guidelines (based on diagnosis, weight, etc) listed in the FDA approved labeling.

C. Medications in this policy used for the treatment of pulmonary arterial hypertension will be considered investigational or experimental for any other use and will not be covered.

D. <u>Reauthorization Criteria:</u>

All prior authorization renewals are reviewed on an annual basis to determine the Medical Necessity for continuation of treatment. Authorization may be extended at 1-year intervals based upon:

<u>MPC Renewal:</u>

- Chart documentation from the prescriber that the member's condition has improved based upon the prescriber's assessment while on therapy.

- Must have chart documentation of clinical response, such as one of the following:
  - Reduction in mPAP of at least 10 mm-Hg from baseline
  - mPAP <40 mmHg without a decrease in cardiac output
  - Improvement on 6-minute walk test from baseline
- For Tracleer less than 18 years old:
  - Must provide documentation of improvement in PVR and/or exercise ability

- Must not have unacceptable toxicity from the drug which requires discontinuation of therapy, such as:
    - Revatio, Adcirca: pulmonary edema; hearing or visual impairment; symptomatic hypotension; epistaxis
    - Flolan, Veletri: anticoagulation abnormalities (bleeding); pulmonary edema
    - Remodulin: blood stream infections (BSIs); sepsis; infusion site reactions
    - Tyvaso: symptomatic hypotension; anticoagulation abnormalities (bleeding)
    - Ventavis: hypotension (systolic BP < 85 mm Hg); pulmonary edema
    - Tracleer, Letairis, Opsumit: hepatic impairment; fluid retention; pulmonary edema; decreased hemoglobin and hematocrit
    - Adempas: symptomatic hypotension, bleeding, and pulmonary edema.
    - Uptravi: decreased hemoglobin
- For Tracleer, Letairis, Opsumit, and Adempas, verification prescriber and patient are enrolled in associated REMS Program
- If patient is a woman of childbearing potential, documented contraceptive plan and negative pregnancy test

Renewal from Previous Insurer:

- Members who have received prior approval (from insurer other than MPC), or have been receiving medication samples, should be considered under criterion A (Initial Authorization Criteria)
- Provider has documented clinical response of the member's condition which has stabilized or improved based upon the prescriber's assessment

Limitations:

Length of Authorization (if above criteria met)	
Initial Authorization	Up to 1 year
Reauthorization	Same as initial

If the established criteria are not met, the request is referred to a Medical Director for review.

Code	Description
J1325	Injection, epoprostenol, 0.5 mg

REFERENCES

1. Wickersham RM, Novak KK, managing eds. Drug Facts and Comparisons. St. Louis, MO: Wolters Kluwer Health, Inc.; 2005.
2. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347:322-329.
3. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Eng J Med. 2004;351:1655-1665.
4. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43(suppl s):5S-12S.
5. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.
6. Sablotzki A, Hentschel T, Gruenig E, et al. Hemodynamic effects of inhaled aerosolized iloprost and inhaled nitric oxide in heart transplant candidates with elevated pulmonary vascular resistance. Eur J Cardiothorac Surg. 2002;22:746-752.
7. Hallioglu O, Dilber E, Celiker A. Comparison of acute hemodynamic effects of aerosolized and intravenous iloprost in secondary pulmonary hypertension in children with congenital heart disease. Am J Cardiol. 2003;92:1007-1009.
8. Olschewski H, Walmrath D, Schermuly R, Ghofrani A, Grimminger F, Seeger W. Aerosolized prostacyclin and iloprost in severe pulmonary hypertension. Ann Intern Med. 1996;124:820-824.
9. Opitz CF, Wensel R, Bettmann M, et al. Assessment of the vasodilator response in primary pulmonary hypertension: comparing prostacyclin and iloprost administered by either infusion or inhalation. Eur Heart J. 2003;24:356-365.
10. Sablotzki A, Czeslick E, Schubert S, et al. Iloprost improves hemodynamics in patients with severe chronic cardiac failure and secondary pulmonary hypertension. Can J Anaesth. 2002;49:1076-1080.
11. Sablotzki A, Czeslick E, Gruenig E, et al. First experiences with the stable prostacyclin analog iloprost in the evaluation of heart transplant candidates with increased pulmonary vascular resistance. J Thorac Cardiovasc Surg. 2003;125:960-962.
12. Theodoraki K, Rellia P, Thanopoulos A, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. Can J Anaesth. 2002;49:963-967.
13. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. Circulation. 2000;101:2388-2392.
14. Blumberg FC, Riegger GA, Pfeifer M. Hemodynamic effects of aerosolized iloprost in pulmonary hypertension at rest and during exercise. Chest. 2002;121:1566-1571.
15. Wiedemann R, Ghofrani A, Weissmann N, et al. Atrial natriuretic peptide in severe primary and nonprimary pulmonary hypertension: response to iloprost inhalation. J Am Coll Cardiol. 2001;38:1130-1136.
16. Leuchte HH, Schwaiblmair M, Baumgartner RA, Neurohr CF, Kolbe T, Behr J. Hemodynamic response to sildenafil, nitric oxide, and iloprost in primary pulmonary hypertension. Chest. 2004;125:580-586.
17. Hoeper MM, Olschewski H, Ghofrani HA, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. J Am Coll Cardiol. 2000;35:176-182.
18. Rimensberger PC, Spahr-Schopfer I, Berner M, et al. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms. Circulation. 2001;103:544-548.
19. Petkov V, Ziesche R, Mosgoeller W, et al. Aerosolized iloprost improves pulmonary haemodynaimcs in patients with primary pulmonary hypertension receiving continuous epoprostenol treatment. Thorax. 2001;56:734-736.
20. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. Ann Intern Med. 2002;136:515-522.
21. Wilkens H, Guth A, Konig J, et al. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. Circulation. 2001;104:1218-1222.

22. Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. J Am Coll Cardiol. 2003;42:158-164.
23. Olschewski H, Rohde B, Behr J, et al. Pharmacodynamics and pharmacokinetics of inhaled iloprost, aerosolized by three different devices, in severe pulmonary hypertension. Chest. 2003;124:1294-1304.
24. Gessler T, Schmehl T, Hoeper MM, et al. Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension. Eur Respir J. 2001;17:14-19.
25. Hoeper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med. 2000;342:1866-1870.
26. CoTherix, Inc. Clinical development. Available at: http://www.cotherix.com/ct/clinical_dev. Accessed February 1, 2005.
27. Machherndl S, Kneussl M, Baumgartner H, et al. Long-term treatment of pulmonary hypertension with aerosolized iloprost. Eur Respir J. 2001;17:8-13.
28. Olschewski H, Ghofrani A, Schmehl T, et al. Inhaled iloprost to treat severe pulmonary hypertension: an uncontrolled trial. Ann Intern Med. 2000;132:435-443.
29. Ghofrani HA, Friese G, Discher T, et al. Inhaled iloprost is a potent acute pulmonary vasodilator in HIV-related severe pulmonary hypertension. Eur Respir J. 2004;23:321-326.
30. Olschewski H, Ghofrani HA, Walmrath D, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med. 1999;160:600-607.
31. Leuchte HH, Baumgartner RA, Behr J. Treatment of severe pulmonary hypertension with inhaled iloprost [letter]. Ann Intern Med. 2003;139:306.
32. Tissieres P, Nicod L, Barazzone-Argiroffo C, Rimensberger PC, Beghetti M. Aerosolized iloprost as a bridge to lung transplantation in a patient with cystic fibrosis and pulmonary hypertension. Ann Thorac Surg 2004;78:e48-50.
33. Halank M, Marx C, Miehlke S, Hoeffken G. Use of aerosolized inhaled iloprost in the treatment of portopulmonary hypertension [letter]. J Gastroenterol. 2004;39:1222-1223.
34. Roig Figueroa V, Herrero Perez A, de la Torre Ferrera N, Hernandez Garcia E, Aller Alvarez JL, Para Cabello J. Iloprost for chronic thromboembolic pulmonary hypertension. Arch Bronconeumol. 2004;40:326-328.
35. Beghetti M, Berner M, Rimensberger PC. Long term inhalation of iloprost in a child with primary pulmonary hypertension: an alternative to continuous infusion. Heart. 2001;86:e10.
36. Schenk P, Petkov V, Madl C, et al. Aerosolized iloprost therapy could not replace long-term IV epoprostenol (prostacyclin) administration in severe pulmonary hypertension. Chest. 2001;119:296-300.
37. Langer F, Wilhelm W, Tscholl D, et al. Intraoperative inhalation of the long-acting prostacyclin analog iloprost for pulmonary hypertension. J Thorac Cardiovasc Surg. 2003;126:874-875.
38. Rex S, Busch T, Vettelschoss M, de Rossi L, Rossaint R, Buhre W. Intraoperative management of severe pulmonary hypertension during cardiac surgery with inhaled iloprost. Anesthesiology. 2003;99:745-747.
39. Kramm T, Eberle B, Krummenauer F, Guth S, Oelert H, Mayer E. Inhaled iloprost in patients with chronic thromboembolic pulmonary hypertension: effects before and after pulmonary thromboendarterectomy. Ann Thorac Surg. 2003;76:711-718.
40. Wittwer T, Pethig K, Struber M, et al. Aerosolized iloprost for severe pulmonary hypertension as a bridge to heart transplantation. Ann Thorac Surg. 2001;71:1004-1006.
41. European Medicines Agency. Ventavis: summary of product characteristics. Available at: http://www.emea.eu.int/humandocs/PDFs/EPAR/ventavis/H-474-PI-en.pdf. Accessed July 28, 2004.
42. Emmel M, Keuth B, Schickendantz S. Paradoxical increase of pulmonary vascular resistance during testing of inhaled iloprost. Heart. 2004;90:e2.
43. Beghetti M, Reber G, de Moerloose P, et al. Aerosolized iloprost induces a mild but sustained inhibition of platelet aggregation. Eur Respir J. 2002;19:518-524.
44. Pharmacy and Therapeutics Review on Ventavis®. Formulary Monograph Service. August 2007.
45. Iloprost. Drugdex Summary in Micromedex.
46. Revatio [sildenafil]. New York, NY: Pfizer Labs: January 2014.

47. Letairis [ambrisentan]. Foster City, CA: Gilead: March 2011.
48. Tracleer [bosentan]. South San Francisco, CA: Actelion Pharmaceuticals, Inc.: February 2007.
49. Flolan [epoprostenol]. Foster City, CA: Gilead: September 2002
50. Remodulin [treprostinil]. Bloomington, IN: Baxter Pharmaceutical Solutions, LLC: March 2006.
51. Ventavis [iloprost]. South San Francisco, CA: CoTherix, Inc.; December 2004.
52. Tyvaso [treprostinil]. Research Triangle Park, NC: United Therapeutics Corp: July 2009.
53. Adcirca [tadalafil]. Indianapolis, IN: Eli Lilly and Company: May 2009.
54. 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. Epub 2009 Mar 30.
55. Rich S, ed. Executive summary from the World Symposium on Primary Pulmonary Hypertension 1998, Evian, France, September 6-10, 1998, cosponsored by the World Health Organization. Available at: http://www.who.int/ncd/cvd/pph.html. Accessed Oct 5,2009.
56. Badesch DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension. *Chest* 2007;131;1917-1928
57. Chin KM, Lewis LJ. Pulmonary arterial hypertension. *J Am Coll Cardiol* 2008;51:1527-38
58. Veletri [package insert]. South San Francisco: Actelion Pharmaceuticals US, Inc.; March 2011
59. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol 2009;54:S43-54*
60. Badesch DB, Champion HC, Sanchez MAG, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54;S55-66
61. Barst RJ, Gibbs SR,, Ghofrani HA, et al. Updated evidenced-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54;S78-84
62. Baim D, ed. *Grossman's Cardiac Catheterization, Angiography, and Intervention.* Lipincott Williams & Wilkins 7th Ed. 2006.
63. Adempas [package insert], Whippany, NJ; Bayer HealthCare Pharmaceuticals, Inc.; October 2013.
64. 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.
65. Hossein-Ardeschir G, Galie N, Grimminger F, et al. *N. Engl. J. Med* 2013; 369;330-40.
66. Piazza G, Goldhaber SZ, Chronic thromboembolic pulmonary hypertension . *N. Engl. J. Med* 2011; 364:351-60.
67. Opsumit [package insert], South San Francisco, CA; Actelion Pharmaceuticals US, Inc.; October 2013.
68. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulomonary arterial hypertension, *N. Engl. J. Med* 2013; 369;809-18.
69. O'Callaghan DS, Savale L, Yaici A, et al. Endothelian receptor antagonists for the treatment of pulmonary arterial hypertension. Expert Opin. Pharmacother 2011:12(10);1585-1596.
70. Orenitram™ [package insert]. Research Triangle Park, NC; United Therapeutics, Corp.; December 2013.
71. Kim NH, Deleroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension, J Am Coll Cardio, 2013;62;D92-9.
72. Uptravi [prescribing information] South San Francisco, CA: Actelion Pharmaceuticals Inc; December 2015.
73. McLaughlin VV, Archer SL, Badesch DB, 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. Journal of the American College of Cardiology. 2009;53(17):1573-1619.

74. 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. 2015
75. Galiè N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. Journal of the American College of Cardiology. 2013;62(25 Suppl):D60-72.

REVIEW HISTORY

DESCRIPTION OF REVIEW / REVISION	DATE APPROVED
Annual Review *Change in Non-MPC renewal to renewal from previous insurer*	*02/2024*
Annual review	*02/2023*
Selected Revision *Addition of MPC vs Non-MPC Renewal*	*10/2022*
Annual review	*02/2022*
Addition of dosing requirements and off-label restrictions	*12/2021*
P&T Review	*11/2020*