Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 08/08/2024

Pulmonary Arterial Hypertension Products

Flolan® (epoprostenol)
Remodulin® (treprostinil)
Tyvaso® (treprostinil)
Uptravi® (selexipag)
Veletri® (epoprostenol)
Winrevair™ (sotatercept-csrk)

HCPCS: Flolan/Veletri: J1325; Remodulin: J3285; Tyvaso: J7686; Uptravi: J3490; Winrevair: J3590

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indication
   b. FDA approved age
   c. If the requested drug is listed below, the member must meet the additional criteria listed:

Drug(s)	Criteria

Tyvaso	• For pulmonary hypertension associated with interstitial lung disease (PH-ILD; World Health Organization (WHO) Group 3) - no further criteria are required.
	• Pulmonary Arterial Hypertension (PAH) WHO Group 1 - trial and failure, intolerance or contraindication to all of the following
	  ○ Generic sildenafil or tadalafil
	  ○ Generic ambrisentan or bosentan

Uptravi injection	• Trial and failure, intolerance or contraindication to all of the following: o Generic sildenafil or tadalafil o Generic ambrisentan or bosentan o Adempas • Currently stable on oral Uptravi therapy • Will be used as short-term bridging therapy in those patients temporarily unable to take oral therapy
Winrevair injection	• Trial and failure, intolerance or contraindication to all of the following: o Generic sildenafil or tadalafil AND o A generic or preferred endothelin receptor antagonist (ERA) • The member will self-administer Winrevair unless clinically unable to do so

d. Trial and failure, contraindication, or intolerance to the preferred drugs as listed in BCBSM/BCN's prior authorization and step therapy documents and/or BCBSM/BCN's utilization management medical drug list

Note: This policy pertains to Medicare Part B only

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time unless specified below
      i. Uptravi injection: 60 days
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit unless specified below.
      i. Uptravi injection: Not applicable as no further authorization will be provided

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- FDA approved indications for medications covered in this policy:

  - Epoprostenol: A prostacyclin vasodilator indicated for the treatment of PAH (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

  - Treprostinil: A prostacyclin vasodilator indicated for:

    - Treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and

etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).

- Patients who require transition from epoprostenol, to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

- Uptravi: A prostacyclin receptor agonist indicated for the treatment of PAH (WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH.

- Winrevair: An activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events.

- CHEST 2019 guideline-supported therapies for WHO Functional Class II and III include: sildenafil, tadalafil, ambrisentan, bosentan, macitentan, riociguat, treprostinil inhalation, and iloprost inhalation.

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- Additional CHEST 2019 guideline-supported therapies for WHO Functional Class III and IV include: epoprostinil IV and treprostinil IV/SQ, and in those who cannot use IV/SQ, treprostinil inhalation and iloprost inhalation.

- PDE5Is and ERAs are clinically effective guideline-supported therapies that have wide utility per CHEST guideline recommendations and are cost effective as they are available as generics.

- Opsumit (macitentan) has no clinical advantages over ambrisentan and bosentan at this time, as all three ERAs are now FDA approved to prevent disease progression and clinical worsening. Ambrisentan and bosentan are more cost effective therapies as they are available generically.

- CHEST 2019 guidelines suggest initial monotherapy with ERA, PDE5I, or Adempas (riociguat) for treatment of WHO Functional Class II or III, and suggest adding a second class if inadequate response to initial monotherapy.

- CHEST 2019 guidelines suggest adding a third drug class in WHO Class III or IV with deterioration.

- CHEST 2019 guidelines suggest inhaled prostacyclins (Tyvaso (treprostinil), Ventavis (iloprost)) for WHO Class III after failure of one or two classes of oral agents.

- The 2022 European Society of Cardiology (ESC) / European Respiratory Society (ERS) clinical guidelines recommend initial combination therapy of an ERA and a PDE5 inhibitor for patients with idiopathic PAH, heritable drug-associated PAH, or PAH-associated with connective tissue disease without cardiopulmonary comorbidities at low or intermediate risk.

- Cross benefit opportunities may exist to step on drugs on the medical benefit for prostacyclin drugs per guidelines, as SQ/IV therapy is preferred to inhalation for WHO Class III and WHO Class IV. Prostacyclin SQ/IV medications may be more cost-effective, however require more complex administration. Further investigation is warranted.

- Uptravi (selexipag) and Orenitram ER (treprostinil tablets) were found to have insufficient clinical evidence to support a guideline recommendation per the CHEST 2019 guidelines. Utilization of guideline supported agents is promoted by step therapy.

- Per package labeling, in Uptravi (selexipag) clinical trials at baseline, 80% of patients were being treated with a stable dose of an ERAs (15%), a PDE5Is (32%), or both (33%).

- Per FDA label, Adempas (riociguat) should not be used in combination with a PDE5I.

- Pulmonary hypertension (PH) with insterstitial lung disease and pulmonary fibrosis can be treated with IV or inhaled treprostinil. PDE5Is have shown little or no benefit in these patients. ERAs, specifically ambrisentan, have been shown to be ineffective and associated with adverse effects in patients with PH while bosentan and macitentan are ineffective in idiopathic pulmonary fibrosis (IPF) but have not been tested in IPF associated PH.

- Uptravi's prospective, multicenter, open-label, single-sequence, cross-over, Phase III study showed the safety, tolerability and pharmacokinetics of temporarily switching between oral Uptravi and Uptravi IV in 20 patients. Patients who were stable on oral Uptravi switched to IV Uptravi for three infusions including the morning and evening dose on Day 1, and morning dose of Day 2 before switching back to the oral formulation in the evening of Day 2.

- Winrevair's Phase III STELLAR trial showed improvement compared to placebo in the 6-minute talk distance of 41 meters at week 24. In this study most participants were receiving either three (61%) or two (35%) background drugs for PAH, and 40% were receiving prostacyclin infusions.

- Dosage modifications of Winrevair due to increased hemoglobin (Hgb) and decreased platelets may be necessary. Hgb and platelets should be checked before each dose for the first 5 doses, or longer if values are unstable, and should be monitored periodically thereafter. Winrevair is intended for use under the guidance of a healthcare professional. Patients and caregivers may administer Winrevair when considered appropriate and when they receive training and follow-up from the healthcare provider (HCP) on how to reconstitute, prepare, measure, and inject Winrevair. Clinical reasons a patient may be unable to self-administer Winrevair include but are not limited to:

    - Patient or caregivers are unable to perform subcutaneous injections with proper technique

    - Member requires monthly medical support from the physician

- Merck will be using two specialty pharmacies to dispense Winrevair in the United States: Accredo Health Group, Inc. and CVS Specialty. Merck has chosen this limited specialty pharmacy network to most efficiently provide access and support to patients. Accredo and CVS Specialty will be supporting patients and physicians by providing education and training for self-administration of Winrevair.

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Policy History		
#	Date	Change Description
2.4	Effective Date: 08/08/2024	Updated criteria for Tracleer suspension from "unable to swallow tablets" to t/f sildenafil or tadalafil AND ambrisentan or bosentan. Removed t/f sildenafil or tadalafil AND ambrisentan or bosentan criteria from Adempas.
2.3	Effective Date: 06/06/2024	Addition of Opsynvi and Winrevair Removed specific Opsumit criteria to reflect what is being implemented
2.1	Effective Date: 06/08/2023	Addition of Liqrev
2.0	Effective Date: 08/04/2022	Updated to add Tyvaso DPI formulation and Tadliq
1.9	Effective Date: 10/10/2021	Annual review of medical policy. Criteria applies to Medicare Part B only.
1.8	Effective Date: 06/10/2021	Updated policy with specific step therapy for certain medications following CHEST 2019 guidelines and included Tyvaso's new indication for PH-ILD; WHO Group 3
1.7	Effective Date: 06/11/2020	Annual Review of Medical Policy
1.6	Effective Date: 06/06/2019	Added trial and failure of preferred products statement
1.5	Effective Date: 02/14/2019	Annual Review of Medical Policy
1.4	Effective Date: 07/05/2017	UM medical management system update for MAPPO and BCNA for Flolan, Remodulin, Tyvaso, Veletri, and Ventavis
1.3	Effective Date: 08/14/2014	Add QL to Orenitram and updated information on dosing, safety, pregnancy & lactation, adverse effects
1.2	Effective Date: 05/08/2014	Criteria Update: Updated to include Orenitram
1.1	Effective Date: 02/06/2014	Criteria Update
1.0	Effective Date: 02/07/2013	Criteria Update

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*