Pulmonary Arterial Hypertension Agents

Policy Number: MC/PC 033
Effective Date: March 1, 2025

Instructions for Use

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Related Policies

- n/a

Coverage Rationale

This policy refers to the following Pulmonary Arterial Hypertension Agents:

- Treprostinil Injection, for intravenous use
- Remodulin (treprostinil) Injection, for intravenous use

Pulmonary Arterial Hypertension (PAH)

For initial coverage of generic treprostinil injection or brand Remodulin injection for Pulmonary Arterial Hypertension, the following will be required:

- Diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1) **and**
- Pulmonary arterial hypertension is symptomatic **and**
- One of the following:
  - Diagnosis of pulmonary arterial hypertension was confirmed by right heart catheterization **or**
  - Patient is currently on any therapy for the diagnosis of pulmonary arterial hypertension **and**
- Prescribed by or in consultation with one of the following:
  - Pulmonologist
  - Cardiologist

For reauthorization coverage of generic treprostinil injection or brand Remodulin injection, the following will be required:

- Patient demonstrates positive clinical response to therapy.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan

document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3285	Injection, treprostinil, 1 mg

ICD-10 Code	Description
I27.0	Primary pulmonary hypertension [not covered for pulmonary artery denervation]
I27.20 - I27.29	Other secondary pulmonary hypertension
J84.111- J84.113	Idiopathic interstitial pneumonia

Background

Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is a chronic, life-threatening disease that is characterized by elevated pressure in the pulmonary arteries due to pulmonary remodeling and increased pulmonary resistance (*Ruopp and Cockrill 2022*). According to the 6th World Symposium on PH, the condition is classified into 5 World Health Organization (WHO) groups (*Simonneau et al 2019*):

- Group 1 – PAH
- Group 2 – PH secondary to left heart disease
- Group 3 – PH secondary to lung diseases and/or hypoxia
- Group 4 – PH due to pulmonary artery obstructions
- Group 5 – PH with unclear and/or multifactorial mechanisms

In addition to the diagnostic classification, patients may be stratified according to their WHO functional capacity (WHO FC), which was adapted from the New York Heart Association (NYHA) classification of left heart failure. A brief description of these functional classes (FC) is as follows (*Stringham et al 2010*):

- Class I: No limitation of physical activity
- Class II: Slight limitation of physical activity
- Class III: Marked limitation of physical activity
- Class IV: Inability to carry out any physical activity without symptoms

Specific agents to treat PAH primarily target pathways critical to its pathobiology including the prostacyclin, endothelin, and nitric oxide pathways (*Wu et al 2013*). There are currently 6 therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (*Lexicomp 2024*). Drugs active within the prostacyclin pathway are the prostacyclin analogues (PCAs) or prostanoids (intravenous [IV] epoprostenol; inhaled iloprost; and IV, subcutaneous [SC], inhaled, and oral treprostinil) and a prostacyclin receptor (IP) agonist (oral and IV selexipag). Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan). Drugs active within the nitric oxide pathway are the phosphodiesterase-type-5 (PDE-5) inhibitors (IV and oral sildenafil and oral tadalafil) and a soluble guanylate cyclase (sGC) stimulator (oral riociguat). Drugs acting as activin signaling inhibitors that bind to activin A and other transforming growth factor (TGF)- β superfamily ligands (sotatercept-csrk) in order to modulate vascular proliferation.

In PAH, prostacyclin synthase is reduced, resulting in inadequate production of prostacyclin I2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (*McLaughlin et al 2009*). Iloprost and treprostinil are PCAs that were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (*Asaki et al 2015*). Iloprost is available as an inhalation solution (Ventavis). Treprostinil is available in several formulations, including an injectable (IV or SC) product (Remodulin), an oral product (Orenitram), and inhalation products (Tyvaso and Tyvaso DPI).

Clinical Evidence

The safety and efficacy of Remodulin were evaluated in 2 identical 12-week, multicenter, randomized, placebo-controlled, double-blind trials in a total of 470 patients with New York Heart Association (NYHA) Class II, III, and IV PAH. Remodulin was administered SC at an average dose of 9.3 ng/kg/min. The effect on the six-minute walk distance (6MWD) was small and did not achieve statistical significance at 12 weeks. For the combined populations, the median change from baseline for patients on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters from a baseline of approximately 345 meters. Remodulin significantly improved the Borg dyspnea score during the 6-minute walk test. Remodulin also consistently improved indices of dyspnea, fatigue, and signs and symptoms of PH. However, these results were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms (*Remodulin prescribing information 2023, Simonneau et al 2002*).

Clinical Guidelines
The Chest Guideline and Expert Panel Report 2019 update on pharmacologic therapy for PAH recommends initial combination therapy rather than monotherapy, which is a change from the 2014 guideline (*Klinger et al 2019*).
With regards to initial therapy, for patients in WHO FC II or III, combination therapy with Letairis (ambrisentan) and Adcirca (tadalafil) is recommended to improve 6MWD. For patients unwilling or unable to take combination therapy, monotherapy with an ERA, PDE-5 inhibitor or soluble guanylate cyclase stimulator (sGC) is recommended. For WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral PCA should be considered. For patients in WHO FC IV, a parenteral PCA is recommended; however, if patients are unable or unwilling to manage a parenteral product, an alternative is an inhaled PCA combined with an ERA and an oral PDE-5 inhibitor. With regards to subsequent therapy, for patients in WHO FC III who have evidence of progression or markers of poor prognosis despite treatment with 1 or 2 classes of oral agents, addition of an inhaled or parenteral prostanoid should be considered. In patients in WHO FC III or IV, if clinical status is unacceptable, a second (and if needed, a third) class of PAH therapy can be added. Due to limited evidence, the guideline does not provide recommendations for or against the use of Orenitram (treprostinil) or Uptravi (selexipag).

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guideline for the diagnosis and treatment of PH *(Humbert et al 2022*) provides treatment recommendations in patients with PAH with and without cardiopulmonary comorbidities (obesity, hypertension, diabetes mellitus, and coronary heart disease). For patients without cardiopulmonary comorbidities, presenting at low or intermediate risk of death, initial oral combination therapy with an ERA and a PDE-5 inhibitor is recommended (Class I recommendation). Specifically, the combinations of Letairis and Adcirca or Opsumit (macitentan) and Adcirca are recommended; other ERAs and PDE-5 inhibitors can also be considered. For patients presenting at high risk of death, initial combination therapy with an ERA, a PDE-5 inhibitor, and a parenteral PCA (IV epoprostenol or IV/SC treprostinil) should be considered (Class IIa recommendation). At follow-up assessments, continuation of initial therapy is recommended in patients at low risk. In patients at intermediate–low risk despite receiving combination therapy with an ERA and a PDE-5 inhibitor, adding Uptravi, or switching from the PDE-5 inhibitor to Adempas (riociguat), should be considered. In patients who are at intermediate–high or high risk while receiving oral therapies, the addition of IV epoprostenol or IV/SC treprostinil and/or evaluation for lung transplantation should be considered. For sequential drug combination therapy, it is recommended to base treatment escalations on risk assessment and general treatment strategies. To reduce the risk of morbidity/mortality events, the following are recommended (Class I recommendations): addition of Opsumit to PDE-5 inhibitors or oral/inhaled PCAs, addition of Uptravi to ERAs and/or PDE-5 inhibitors, and addition of Orenitram to ERA or PDE-5 inhibitor/Adempas monotherapy. To improve exercise capacity, the addition of sildenafil to epoprostenol is recommended (Class I recommendation). In patients with cardiopulmonary comorbidities (low, intermediate, or high risk of death), initial oral monotherapy with an ERA or a PDE-5 inhibitor should be considered (Class IIa recommendation). At follow-up assessments, in patients presenting at intermediate or high risk of death while receiving ERA or a PDE-5 inhibitor monotherapy, additional agents for PAH may be considered on an individual basis.

A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor

agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.

Reputable society groups agree that evidence supporting pediatric treatment is lacking. The AHA and American Thoracic Society (ATS) published a guideline on pediatric PH. This guideline states that in pediatric patients with lower-risk PAH, oral therapy with either a PDE-5 inhibitor or an ERA is recommended, and in pediatric patients with higher-risk PAH, IV or SC PCAs should be initiated without delay (*Abman et al 2015*). An expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network (endorsed by the Association for European Pediatric and Congenital Cardiology, the European Society for Pediatric Research, and the International Society of Heart and Lung Transplantation) recommends a PDE-5 inhibitor, ERA, or oral/inhaled prostacyclin agonist therapy for pediatric patients with low- or intermediate-risk PAH. Initial combination therapy with a PDE-5 inhibitor and an ERA may be considered for patients who are at intermediate risk. Higher-risk patients should be treated with IV epoprostenol or IV or SC treprostinil; early combination therapy with a PDE-5 inhibitor, an ERA, and a PCA may also be considered in these patients *(Hansmann et al 2019*).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Remodulin (treprostinil injection) is a prostacyclin mimetic indicated for:

- Treatment of pulmonary arterial hypertension (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.

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Policy History/Revision Information

Date	Summary of Changes
3/20/2024	Approved by OptumRx P&T Committee
2/20/2025	Annual review. Updated background, clinical guidelines and references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Archived Policy Versions (Internal Only)

Effective Date	Policy Number	Policy Title
mm/dd/yyyy – mm/dd/yyyy	######	Title of Policy Hyperlinked to KL or Other Internal Location

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

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Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).

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