Medical Policy Bulletin

Title:
Treatment of Pulmonary Artery Hypertension with Intravenous, Subcutaneous, and Inhaled Pharmacologic Agents
Policy #:
MA08.016h

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

This policy uses coverage criteria primarily based on applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals and other applicable Medicare coverage documents. In the absence of fully established coverage criteria from these Medicare coverage documents for a specific medical service or item, the criterion/indication/service indicated by an asterisk below (**) is based on internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, regulatory status, and/or expert opinion.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

COMPANY-DESIGNATED PREFERRED PRODUCTS

Although there are many generic treprostinil sodium products on the market, there is no reliable evidence of the superiority of any one product of treprostinil sodium over another. The Company has designated the Sandoz treprostinil sodium product as its preferred product.

These products are less costly and at least as likely to produce equivalent therapeutic results as the nonpreferred products, which include, but are not limited to, treprostinil sodium manufactured by other companies.

NON-PREFERRED PRODUCTS

Use of the nonpreferred generic treprostinil sodium products, which include but are not limited to manufacturers other than Sandoz, is considered medically necessary and, therefore, covered only for individuals who are currently receiving or have previously received a nonpreferred product.

If the individual has not previously received Sandoz treprostinil sodium to treat the specified indication, these nonpreferred products are only eligible for coverage when the individual has contraindication(s) or intolerance(s) to the Company-designated preferred product.

EPOPROSTENOL (FLOLAN®, VELETRI®) ** (FDA, 2020)
Epoprostenol (Flolan®, Veletri®), intravenous infusion, is considered medically necessary and, therefore, covered when the dosing and frequency requirements listed in Attachment A and all of the following criteria are met:

- The individual has a confirmed diagnosis of pulmonary arterial hypertension (PAH), in accordance with the World Health Organization (WHO) Group 1 classification.
    - The diagnosis of PAH has been confirmed by a catheterization (right heart or Swan-Ganz) or echocardiography.
- Documentation of all of the following: **(Maron, 2023)
    - Individual's mean pulmonary arterial pressure is greater than 20 mm Hg
    - The pulmonary capillary wedge pressure or left ventricular end-diastolic pressure is 15 mm Hg or less
    - Pulmonary vascular resistance (PVR) is greater than 2.0 Woods Units (WU)
- The individual meets the New York Heart Association (NYHA) Functional Classification requirement of Class III-IV.

TREPROSTINIL SODIUM (REMODULIN®) ** (FDA, 2023)
Treprostinil sodium (Remodulin®)*, intravenous or subcutaneous infusion, is considered medically necessary and, therefore, covered when the dosing and frequency requirements listed in Attachment A and all of the following criteria are met:

- The individual has a confirmed diagnosis of PAH, in accordance with the WHO Group 1 classification.
    - The diagnosis of PAH has been confirmed by a catheterization (right heart or Swan-Ganz) or echocardiography
- Documentation all of the following: **(Maron, 2023.)
    - Individual's mean pulmonary arterial pressure is greater than 20 mm Hg
    - The pulmonary capillary wedge pressure or left ventricular end-diastolic pressure is 15 mm Hg or less
    - PVR is greater than 2.0 WU
- The individual meets the NYHA Functional Classification requirement of Class II-IV

*In addition, treprostinil sodium (Remodulin®), intravenous or subcutaneous infusion, is considered medically necessary and, therefore, covered for individuals requiring transition from epoprostenol (Flolan®) to diminish the rate of clinical deterioration. Clinical deterioration is defined as an increase in epoprostenol (Flolan®) dose, hospitalization due to PAH.

ILOPROST (VENTAVIS®)
Iloprost (Ventavis®) inhalation is considered medically necessary and, therefore, covered when the dosing and frequency requirements listed in Attachment A and all of the following criteria are met:

- The individual has a diagnosis of pulmonary artery hypertension (PAH) and the pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left-sided atrial or ventricular disease, left-sided valvular heart disease) or disorders of the respiratory system (e.g., chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea or other sleep disordered breathing, alveolar hypoventilation disorders)
- The individual has primary pulmonary hypertension or pulmonary hypertension, which is secondary to conditions that include, but are not limited to, the following: connective tissue disease, human immunodeficiency virus (HIV) infection, cirrhosis, anorexigens (i.e., diet drugs), or congenital left-to-right shunts. If these conditions are present, all of the following criteria must be met:
    - The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition
    - The mean pulmonary artery pressure is greater than 20 mm Hg. **(Maron, 2023)
    - The individual has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope)
    - Treatment with oral calcium channel blocking agents has been tried and failed, or has been considered and ruled out

TREPROSTINIL (TYVASO®)
Treprostinil (Tyvaso®) inhalation is considered medically necessary and, therefore, covered when the dosing and frequency requirements listed in Attachment A and either of the following criteria are met:

- The individual meets all of the following criteria:
    - The individual has a diagnosis of PAH and the pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left-sided atrial or ventricular disease, left-sided valvular heart disease) or disorders of the respiratory system other than interstitial lung disease (e.g., chronic obstructive pulmonary disease, obstructive sleep apnea or other sleep disordered breathing, alveolar hypoventilation disorders).
    - The individual has primary pulmonary hypertension or pulmonary hypertension, which is secondary to conditions that include, but are not limited to, the following: connective tissue disease, HIV infection, cirrhosis, anorexigens (i.e., diet drugs), or congenital left-to-right shunts. If these conditions are present, all of the following criteria must be met:
        - The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition
        - The mean pulmonary artery pressure is greater than 20 mm Hg at rest or greater than 30 mm Hg with exertion. **(Maron, 2023.)
        - The individual has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope)
        - Treatment with oral calcium channel–blocking agents has been tried and failed, or has been considered and ruled out
    - The individual has a diagnosis of pulmonary hypertension associated with interstitial lung disease and all of the following criteria are met:
        - The presence of interstitial lung disease has been confirmed by a high-resolution computed topography (CT) scan of the chest
        - The mean pulmonary artery pressure is 20 mm Hg or greater **(Maron, 2023.)
        - The pulmonary capillary wedge pressure or left ventricular end-diastolic pressure is 15 mm Hg or less
        - The PVR is 2 WU or greater at rest
        - The individual has significant symptoms of pulmonary hypertension (e.g., dyspnea on exertion, fatigability)

SILDENAFIL (REVATIO®) ** (FDA, 2023)
Sildenafil (Revatio®), intravenous infusion for continued treatment of individuals who are currently prescribed oral sildenafil (Revatio®) and who are temporarily unable to take oral medication, is considered medically necessary and, therefore, covered, when the dosing and frequency requirements listed in Attachment A are met.

SELEXIPAG (UPTRAVI®) ** (FDA, 2021)
Selexipag (Uptravi®) intravenous infusion for continued treatment of individuals who are currently prescribed oral selexipag (Uptravi®) and who are temporarily unable to take oral medication, is considered medically necessary and, therefore, covered, when the dosing and frequency requirements listed in Attachment A are met.

EXPERIMENTAL/INVESTIGATIONAL ** (FDA, 2021, 2023, 2020)

All other uses for epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); sildenafil (Revatio®), and selexipag (Uptravi®); are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the medical policy on off-label coverage for prescription drugs and biologics.

Although the US Food and Drug Administration (FDA) has approved a fully implantable intravenous infusion pump system used to deliver pharmacological agents (prostanoids) for the treatment of PAH, the Company has determined that the safety and/or effectiveness of this device cannot be established by review of the available published peer-reviewed literature. Therefore, a fully implantable intravenous infusion pump system used to deliver pharmacological agents (prostanoids) for the treatment of PAH is considered experimental/investigational by the Company and not covered.

NOT ELIGIBLE FOR SEPARATE REIMBURSEMENT

The Company covers the use of intravenous (IV) fluids for the preparation (e.g., dilution, reconstitution) of pharmaceuticals, biologics, and other substances for IV administration; however, such use is considered to be integral to the administration of the pharmaceutical, biologic, or other substance and is, therefore, not eligible for separate reimbursement. Participating providers may not bill members for this service.

DOSING AND FREQUENCY REQUIREMENTS

Refer to Attachment A for dosing and frequency requirements for epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); sildenafil (Revatio®), and selexipag (Uptravi®).

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this Policy to ensure consistency with the most recently published recommendations for the use of epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); sildenafil (Revatio®), and selexipag (Uptravi®). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the FDA; Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); sildenafil (Revatio®), and selexipag (Uptravi®) outside of the Dosing and Frequency Requirements listed in this Policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the precertification process. The Company reserves the right to conduct postpayment review and audit procedures for any claims submitted for epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); and treprostinil (Tyvaso®); sildenafil (Revatio®), and selexipag (Uptravi®).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug**.**

Guidelines

There is no Medicare coverage determination addressing this service; therefore, the Company policy is applicable.

The World Health Organization (WHO) Group 1 Classification

Pulmonary arterial hypertension (PAH) represents Group 1 within the Pulmonary Hypertension World Health Organization (WHO) clinical classification system and is one of five such groups. The groups are divided based on etiology.

- Idiopathic (IPAH): a rare form of PAH characterized by elevated pulmonary artery pressure with no apparent cause.
- Heritable (HPAH): a form of PAH caused by predisposing genes or from a familial context.
    - Bone morphogenetic protein receptor type 2 (BMPR2)
    - Activin receptor-like kinase 1 gene (ALK1), endoglin (with or without hemorrhagic telangiectasia)
    - Unknown
- Drug- and toxin-induced
- Associated with (APAH)
    - Connective tissue diseases
    - Human immunodeficiency virus (HIV) infection
    - Portal hypertension
    - Congenital heart disease (CHD)
    - Schistosomiasis
    - Chronic hemolytic anemia
- Persistent pulmonary hypertension of the newborn (PPHN)

Group 1

- Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

The New York Heart Association (NYHA) Functional Classifications are summarized as follows:

Class I: Individuals with no limitation of physical activity and no symptoms. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnea (shortness of breath).

Class II: Individuals with slight limitation of physical activity and mild symptoms. Comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.

Class III: Individuals with marked limitation of physical activity due to symptoms. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations, dyspnea, or anginal pain.

Class IV: Individuals with severe limitations experience symptoms of heart failure or the anginal syndrome that may be present even while at rest. If any physical activity is undertaken, discomfort is increased.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); and sildenafil (Revatio®) are covered under the medical benefit of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

Certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); sildenafil (Revatio®), and selexipag (Uptravi®) are covered under the member's medical benefit (Part B benefit). It does not address instances when epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); and sildenafil (Revatio® sildenafil (Revatio®), and selexipag (Uptravi®) are covered under a member's pharmacy benefit (Part D benefit).

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

All pharmacologic agents listed in this medical policy have US Food and Drug Administration approval for the treatment of PAH.

PEDIATRIC USE

The safety and effectiveness of epoprostenol (Flolan®) (Veletri®); treprostinil sodium (Remodulin®); iloprost (Ventavis®); treprostinil (Tyvaso®); and selexipag (Uptravi®) have not been established in the pediatric population. The safety and effectiveness of sildenafil (Revatio®) in the pediatric population has not been established for administration via intravenous bolus injection.

Description

DESCRIPTION AND ETIOLOGY OF PULMONARY ARTERIAL HYPERTENSION (PAH)

Pulmonary arterial hypertension (PAH) (also referred to as pulmonary hypertension [PH] or primary or secondary pulmonary hypertension [PPH, SPH]) is a progressive disorder characterized by abnormally high blood pressure (hypertension) in the pulmonary artery (PA), which carries blood from the heart to the lungs. Hypertension occurs when most of the small arteries throughout the lungs narrow in diameter, increasing resistance to blood flow through the lungs. To overcome the increased resistance, pressure intensifies in the PA and in the right ventricle that pumps blood into the PA. The right side of the heart is forced to work harder against this increased pressure, and, over time, this heightened work load causes the right side of the heart to become enlarged and can progress to right-sided heart failure (cor pulmonale). The National Institutes of Health (NIH) registry working group has defined PAH as a mean PA pressure greater than 25 mm Hg at rest or 30 mm Hg with exercise and no known or proven etiology. There are two main methods used **to measure PA pressures: transthoracic echocardiogram (TTE) and right heart**

catheterization.

Signs and symptoms of the presence of PAH occur when increased pressure cannot fully overcome the elevated resistance, resulting in insufficient blood flow to the body and its organs. The most frequently reported symptom of PAH is dyspnea of exertion (DOE), and the person may report periods of fainting. As the condition worsens, other symptoms, such as dizziness, swelling (edema) of the ankles or legs, overall muscle weakness, chest pain, cyanosis of the skin and/or lips, and heart palpitations, are reported.

THE WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF PULMONARY HYPERTENSION (PH)

PAH is one subset of the larger disease category of pulmonary hypertension (PH). PH is a general term used to describe a chronic, progressive condition characterized by high pulmonary vascular pressure in the lungs. The WHO developed a five-group classification system for PH based on disease etiology. The individuals in WHO Group 1 are considered to have PAH, whereas those in the remaining Group 2–Group 5 are considered to have PH. However, when the groups are discussed collectively, the term PH is used.

OVERALL TREATMENT OF PAH

The treatment of PAH is highly individualized. The goals of PAH treatment consist of symptom improvement, enhanced functional capacity, reversal or prevention of disease worsening, and prevention of hospitalization. Therapy to control PAH consists of diet, exercise, and pharmacologic treatment. Oxygen and medications such as anticoagulants, diuretics, and digoxin are used initially to treat the underlying cause of PAH. In more advanced disease, medications such as calcium channel blockers, intravenous (IV) or inhaled prostanoids (e.g., epoprostenol), endothelin receptor antagonists (e.g., bosentan), or phosphodiesterase-5 (PDE-5) inhibitors (e.g., sildenafil) are used as monotherapy or in combination.

AGENTS ADMINISTERED VIA INTRAVENOUS ROUTE

EPOPROSTENOL (FLOLAN®)
Epoprostenol (Flolan®) is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation. It is indicated for the treatment of PAH (WHO Group 1) to improve exercise capacity in individuals with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

EPOPROSTENOL (VELETRI®)
Veletri® (epoprostenol) is a potent vasodilator intended for the treatment of PAH to improve exercise capacity. During clinical trials, data demonstrating efficacy was obtained predominantly from individuals with NHYA Functional Class III-IV symptoms with etiology from idiopathic or inherited PAH or PAH associated with connective tissue diseases. Veletri® (epoprostenol) is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump.

SILDENAFIL (REVATIO®)
Sildenafil (Revatio®) is a PDE-5 inhibitor indicated for the treatment of PAH (WHO Group I) in adult individuals to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately individuals with NYHA Functional Class II-III symptoms. Etiologies were idiopathic (71 percent) or associated with connective tissue disease (25 percent). Sildenafil (Revatio®) may be administered orally or by injection. Intravenous infusion is for the continued treatment of individuals with PAH who are currently prescribed oral sildenafil (Revatio®) and who are temporarily unable to take oral medication.

SELEXIPAG (UPTRAVI®)

Selexipag (Uptravi®) is a prostacyclin receptor agonist indicated for the treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. The seminal clinical trial for effectiveness was performed predominately in individuals with WHO functional class numbers II and III (43.8% and 54.0%, respectively), equivalent to NYHA Functional Class II-III. Intravenous infusion is for the continued treatment of individuals with PAH who are currently prescribed oral selexipag (Uptravi®) and who are temporarily unable to take oral therapy.

AGENTS ADMINISTERED VIA INTRAVENOUS OR SUBCUTANEOUS INFUSION

TREPROSTINIL (REMODULIN®)
Treprostinil (Remodulin®) is a prostacyclin that causes direct vasodilation of pulmonary and systemic arterial vascular

beds and inhibition of platelet aggregation. It is indicated in the treatment of PAH (WHO Group 1) in individuals with NYHA Class II-IV symptoms. Treprostinil (Remodulin®) is administered as a continuous infusion via a self-inserted subcutaneous catheter using an infusion pump designed for subcutaneous drug delivery. Continuous subcutaneous infusion (undiluted) is the preferred mode of delivery. Intravenous infusion (with dilution required), is reserved for those who cannot tolerate continuous subcutaneous infusion.

Treprostinil (Remodulin®) was originally approved for administration by continuous subcutaneous and intravenous routes using external pumps. Medtronic Inc. (Minneapolis, MN) and United Therapeutics Corp. (Research Triangle Park, NC) received FDA approval for the Implantable System for Remodulin®. The system is composed of the SynchroMed II Pump programmable implantable drug-delivery system and a newly developed intravascular catheter to deliver treprostinil (Remodulin) intravenously for adults with PAH (Class I, II, and III) who were receiving treprostinil (Remodulin®) via continuous intravenous infusion with an external infusion pump. The FDA approval was based on data reported from the DellVery for Pulmonary Arterial Hypertension (PAH) clinical study, a prospective, single-arm, nonrandomized, open-label multicenter study (Waxman et al., 2017). The trial enrolled 64 adults with PAH (WHO group 1); four individuals exited the study prior to device implantation, and the remaining 60 individuals had successful implant procedures. The study showed the implantable intravascular delivery system was an effective option for delivery of treprostinil (Remodulin®), with a low rate of catheter-related complications, and a high rate of individual satisfaction. Clinically significant implant procedure-related complications included one pneumothorax, two infections unrelated to catheter placement, and one episode of atrial fibrillation. Three catheter dislocations in two individuals occurred early in the trial; catheters were removed and replaced via surgical procedure. Larger well-designed studies with long-term follow-up are needed to determine safety and effectiveness of fully implantable intravenous pumps used to deliver pharmacological agents (prostanoids) for the treatment of pulmonary hypertension.

AGENTS ADMINISTERED VIA INHALATION

ILOPROST (VENTAVIS®) INHALATION SOLUTION
Ventavis® (iloprost) inhalation solution is indicated for the treatment of PAH to improve exercise tolerance and NYHA symptoms and prevent deterioration. During clinical trials, data demonstrating efficacy was obtained mostly from individuals with NYHA Functional Class III-IV symptoms who had idiopathic or inherited PAH or PAH associated with connective tissue diseases. Ventavis (iloprost) is administered via an I-neb® Adaptive Aerosol Delivery (AAD) system typically obtained from a specialized pharmacy. The I-neb® ADD nebulizer is not the same type of device that is commonly used to deliver nebulized medications for conditions such as asthma.

TREPROSTINIL (TYVASO®) INHALATION SOLUTION
Treprostinil (Tyvaso) inhalation solution is a prostacyclin vasodilator indicated for the treatment of PAH (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately individuals with NHYA Functional Class III symptoms with etiologies of idiopathic or inherited PAH or PAH associated with connective tissue diseases. Treprostinil (Tyvaso) is given by oral inhalation only via a special nebulizing device, the Optineb®, and its accessories; the Optineb is typically obtained from a specialized pharmacy. The Optineb is not the same type of device that is commonly used to deliver nebulized medications for conditions such as asthma.

Treprostinil (Tyvaso) inhalation solution was investigated in a 16-week, randomized, double-blind, placebo-controlled, multicenter study (INCREASE) that enrolled 326 individuals with PH-ILD. Enrolled study individuals predominately had etiologies of idiopathic interstitial pneumonia inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema, and WHO Group 3 connective tissue disease. The mean baseline 6-minute walk distance (6MWD) was 260 meters. Individuals were randomly assigned (1:1) to either placebo or treprostinil (Tyvaso) and received four daily treatment sessions with a target dose of nine breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the course of the 16-week study. Approximately 75% of individuals randomly assigned to treprostinil (Tyvaso) were titrated up to a dose of nine breaths, four times daily or greater, with 48% of individuals randomly assigned to treprostinil (Tyvaso) reaching a dose of 12 breaths, four times daily during the study. The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to week 16. Secondary endpoints included the change in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level at week 16 and the time to clinical worsening.

l (Tyvaso) group and the placebo group in the change from baseline in the 6MWD was 31.12 m (95% confidence interval [CI], 16.85–45.39; *P*<0.001). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil (Tyvaso) as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47–0.72; *P*<0.001). Clinical worsening occurred in 37 individuals (22.7%) in the treprostinil (Tyvaso) group as compared with 54 individuals (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40–0.92; *P*=0.04 by the log-rank test). The most common adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea.

COMPARISON OF PRODUCTS

Drug	Route of Administration	NYHA Functional Class Symptoms
Flolan (epoprostenol)*	Continuous intravenous infusion	Class III and Class IV
Veletri (epoprostenol)*	Continuous intravenous infusion	Class III and Class IV
Remodulin (treprostinil)*	Continuous intravenous or subcutaneous infusion	Class II, Class III, Class IV
Ventavis Inhalation Solution (iloprost)*	Inhaled	Class III and Class IV
Tyvaso Inhalation Solution (treprostinil)*	Inhaled	Class III
Sildenafil (Revatio®)†	Oral or intravenous bolus injection	Class II and Class III
	Oral or intravenous infusion	Class II, Class III, Class IV

*Safety and effectiveness in the pediatric population have not been established.

†Safety and effectiveness in the pediatric population has not been established for administration via intravenous bolus injection.

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
Report the most appropriate diagnosis code in support of medically necessary criteria as listed in the policy.

HCPCS Level II Code Number(s)
MEDICALLY NECESSARY

J1325 Injection, epoprostenol, 0.5 mg

J3285 Injection, treprostinil, 1 mg

J7686	Treprostinil, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, 1.74 mg
Q4074	Iloprost, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, up to 20 mcg

THE FOLLOWING CODES ARE USED TO REPRESENT SILDENAFIL (REVATIO®) AND **SELEXIPAG (UPTRAVI®)** WHEN ADMINISTERED THROUGH INTRAVENOUS INFUSION:

C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs

NOT ELIGIBLE FOR SEPARATE REIMBURSEMENT

S0155	Sterile dilutant for epoprostenol, 50 ml

EXPERIMENTAL/INVESTIGATIONAL

THE FOLLOWING SERVICES ARE CONSIDERED EXPERIMENTAL/INVESTIGATIONAL WHEN REPORTED WITH J1325, J3285, S0155:

C1751	Catheter, infusion, inserted peripherally, centrally or midline (other than hemodialysis)
C1772	Infusion pump, programmable (implantable)
E0783	Infusion pump system, implantable, programmable (includes all components, e.g., pump, catheter, connectors, etc.)
E0786	Implantable programmable infusion pump, replacement (excludes implantable intraspinal catheter)

Revenue Code Number(s)

N/A

Cross Reference

Treatment of PAH with IV,SC, and Inhalec

Attachment A:
Description: Dosing and Frequency Requirements

Policy History

Revisions From MA08.016h:

06/13/2025	This version of the policy will become effective 06/13/2025. This policy was updated to communicate the following: • Changes in definition for pulmonary arterial hypertension (PAH) due to new/improved outcomes based on early initiation of the therapy.

	All of the ICD-10 CM codes have been removed from this policy, since they are informational The following ICD-10 codes have been removed from this policy: I27.0 Primary pulmonary hypertension I27.20 Pulmonary hypertension, unspecified I27.21 Secondary pulmonary arterial hypertension I27.22 Pulmonary hypertension due to left heart disease I27.24 Chronic thromboembolic pulmonary hypertension I27.29 Other secondary pulmonary hypertension

Revisions From MA08.016g:

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
01/01/2024	This version of the policy will become effective 01/01/2024. This policy was updated to communicate the following: • Medically necessary position for intravenous selexipag (Uptravi®). • Revised medically necessary criteria for treprostinil (Tyvaso®) and Iloprost (Ventavis®) in accordance with LCD 33370. • Removal of medically necessary criteria for sildenafil (REVATIO®) Dosing and frequency requirements were updated for selexipag (Uptravi®) and revised for sildenafil (Revatio®) in the Attachment A of this policy. The following ICD CM codes have been deleted from this policy: J84.10 Pulmonary fibrosis, unspecified J84.111: Idiopathic interstitial pneumonia, not otherwise specified J84.112: Idiopathic pulmonary fibrosis J84.848: Other interstitial lung diseases of childhood J84.89: Other specified interstitial pulmonary diseases J84.9: Interstitial pulmonary disease, unspecified I27.23: Pulmonary hypertension due to lung diseases and hypoxia P29.30: Pulmonary hypertension of newborn

Revisions From MA08.016f:

05/04/2022	This policy has been reissued in accordance with the Company's annual review process.
11/22/2021	This version of the policy will become effective 11/22/2021. The policy was updated to communicate coverage criteria, for treprostinil (Tyvaso®), inhalation for pulmonary hypertension associated with interstitial lung disease (PH-ILD) consistent with the US Food and Drug Administration (FDA) labeling. Dosing and frequency requirements were updated for treprostinil (Tyvaso®) in the Attachment A of this policy. The Company has designated the **Sandoz** treprostinil sodium product as its preferred product.

Revisions From MA08.016e:

12/02/2020	This policy has been reissued in accordance with the Company's annual review process.
01/01/2020	This version of the policy will become effective 01/01/2020. The policy was updated to communicate coverage criteria, for sildenafil (Revatio®), intravenous infusion for pulmonary arterial hypertension (PAH) consistent with the US Food and Drug Administration (FDA) labeling. The following HCPCS codes have been **added** to this policy to represent sildenafil (Revatio®) IV injection: C9399 Unclassified drugs or biologicals J3490 Unclassified drugs

	Dosing and frequency requirements were added for all the agents to Attachment A of this policy.

Revisions From MA08.016d:

05/06/2019	This version of the policy will become effective 05/06/2019. This policy was updated to communicate the following: • Company's position of experimental/investigational for a fully implantable, intravenous drug delivery system for individuals with pulmonary arterial hypertension. • Additon of criteria for Treprostinil sodium (Remodulin®), intravenous or subcutaneous infusion when the individual requires transition from Flolan® to diminish the rate of clinical deterioration. The following HCPCS codes have been **removed** from this policy: S9061 Home administration of aerosolized drug therapy (e.g., Pentamidine); administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment (drugs and nursing visits coded separately), per diem S9347 Home infusion therapy, uninterrupted, long-term, controlled rate intravenous or subcutaneous infusion therapy (e.g., epoprostenol); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem The following HCPCS codes have been **added** to this policy and are considered experimental/investigational when reported with J1325, J3285, S0155: C1772 Infusion pump, programmable (implantable) C1751 Catheter, infusion, inserted peripherally, centrally or midline (other than hemodialysis) E0783 Infusion pump system, implantable, programmable (includes all components, e.g., pump, catheter, connectors, etc.) E0786 Implantable programmable infusion pump, replacement (excludes implantable intraspinal catheter)

Revisions From MA08.016c:

10/01/2017	This policy has been identified for the ICD-10 CM code update, effective 10/01/2017. The following ICD-10 CM codes have been **termed** from this policy: I27.2 Other secondary pulmonary hypertension P29.3 Persistent fetal circulation The following ICD-10 CM codes have been **added** to this policy: I27.20 Pulmonary hypertension, unspecified I27.21 Secondary pulmonary arterial hypertension I27.22 Pulmonary hypertension due to left heart disease I27.23 Pulmonary hypertension due to lung diseases and hypoxia I27.24 Chronic thromboembolic pulmonary hypertension I27.29 Other secondary pulmonary hypertension I27.83 Eisenmenger's syndrome P29.30 Pulmonary hypertension of newborn

Revisions From MA08.016b:

05/26/2017	This policy was updated to clarify the Company's coverage criteria for the treatment of pulmonary artery hypertension with intravenous, subcutaneous, and inhaled pharmacologic agents.

Revisions From MA08.016a:

02/11/2015	This policy has been reviewed and issued to communicate the Company's continuing coverage position on the Treatment of Pulmonary Artery Hypertension with Intravenous, Subcutaneous, and Inhaled Pharmacologic Agents Intended for Home Use. Information regarding the overall treatment of PAH was added to this Policy.

Revisions From MA08.016:

01/01/2015	This is a new policy.

Version Effective Date:
06/13/2025
Version Issued Date:
06/13/2025
Version Reissued Date:
N/A