MEDICAL POLICY STATEMENT		
Effective Date	**Next Annual Review Date**	**Last Review / Revision Date**
06/15/2011	**06/15/2012**	**06/15/2011**
Author		
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CareSource

CSMG Medical Policy Statements are derived from literature based and supported clinical guidelines, nationally recognized utilization and technology assessment guidelines, other medical management industry standards, and published MCO clinical policy guidelines. Medically necessary services are those health care services or supplies which are proper and necessary for the diagnosis or treatment of disease, illness, or injury and without which the patient can be expected to suffer prolonged, increased or new morbidity, impairment of function, dysfunction of a body organ or part or significant pain and discomfort. These services meet the standards of good medical practice in the local area, are the lowest cost alternative and are not provided mainly for the convenience of the member or provider.

A. SUBJECT

Peripheral Vasodilators

- **Treprostinil (Remodulin) Infusion**
- **Treprostinil (Tyvaso) Inhalation**
- **Epropostenol (Flolan, Veletri) Infusion**
- **Iloprost (Ventavis) Inhalation**

B. BACKGROUND

Treprostinil (Remoduilin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri), are synthetic analogs of prostacyclin. A disregulation of the prostacyclin metabolic pathway has been shown in patients with pulmonary arterial hypertension (PAH). This can lead to narrowing of the pulmonary arteries, resulting in increased pulmonary vascular resistance and right heart failure. The pharmacologic actions of prostacyclin analog, act on this pathway resulting in direct vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

The patient selection criteria outlined was derived from the FDA-approved prescribing information for treprostinil (Remoduilin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri), the studies that were presented to the FDA in support of the pre-market approval application, and studies in the peer-reviewed published medical literature. The FDA label indication found in the manufacturer prescribing information and described below is pulmonary arterial hypertension. Coverage decisions for conditions other than the above FDA- approved indications will be reviewed on a case-by-case basis if proven effective through research documentation. The requesting provider will need to support his exception request with the appropriate literature.

Treprostinil (Remoduilin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri) are considered experimental and investigational and does not meet the definition of medical necessity for the treatment of: **Raynaud phenomenon**

C. Policy

CareSource will approve the use of treprostinil (Remodulin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri), and consider their use as medically necessary when the following criteria have been met for:

- Pulmonary arterial hypertension

Pulmonary Arterial Hypertension

Treprostinil (Remodulin) is indicated for the 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%).

Treprostinil (Tyvaso) is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

Iloprost (Ventavis) is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

Epropostenol (Flolan, Veletri) is indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy

Prior Authorization Criteria:

- Documented diagnosis of pulmonary arterial hypertension
    - WHO Group 1 with NYHA Functional class II or III or IV symptoms.
    - PAP pressures not adequately controlled using an oral vasodilator (e.g. calcium channel blockers) at maximal doses
      OR
    - The member was not vasodilator sensitive as determined by a epoprostenol, adenosine, or inhaled nitric oxide challenge
- Patient must be 18 years or older
- Prescribed by a pulmonologist and/or cardiologist or under recommendation of pulmonologist and/or cardiologist

NOTE: In patients with pulmonary arterial hypertension requiring transition from Flolan (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

NOTE: The infusions listed above may be administered as a continuous subcutaneous infusion or continuous intravenous infusion. However, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.

NOTE: Documented diagnosis must be confirmed by portions of the individual's medical record which will confirm the presence of disease and will need to be supplied with prior authorization request. These medical records may include, but not limited to test reports, chart notes from provider's office or hospital admission notes.

Functional Assessment of Pulmonary Arterial Hypertension

New York Heart Association functional classification	
Class 1:	No symptoms with ordinary physical activity.
Class 2:	Symptoms with ordinary activity. Slight limitation of activity.
Class 3:	Symptoms with less than ordinary activity. Marked limitation of activity.
Class 4:	Symptoms with any activity or even at rest.
World Health Organization functional assessment classification	
Class I:	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II:	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III:	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV:	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

For Special Needs Plan members, reference the below link to search for Applicable National Coverage Descriptions (NCD) and Local Coverage Descriptions (LCD):

For Medicare

NCD for treprostinil (Remodulin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri)

Medicare does not have a National Coverage Determination (NCD) for treprostinil (Remodulin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri). In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, section 50 Drugs and Biologicals at: http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf. Local Coverage Determinations (LCDs) for treprostinil (Remodulin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri) do not exist at this time. (Accessed May 9, 2011)

Safety

CareSource will only review requests for **treprostinil (Remodulin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri)** if the patient has **none** of the following contraindications:

- Hypersensitivity to treprostinil, iloprost and epropostenol
- Patient has a diagnosis or Chronic Obstructive Pulmonary Disease (COPD)
- Patient has a diagnosis of severe asthma
- Patient has had a lung resection
- Patients with congestive heart failure
- Patients with pulmonary veno-occlusive disease
- Combination therapy with other PAH agents such as Flolan, another endothelin receptor antagonists, Remodulin, Revatio, Ventavis
- Use in World Health Organization (WHO) group II with pulmonary htn associated with:
    - left heart disease including left-sided atrial or ventricular heart disease
    - left-sided valvular heart disease)
- Use in World Health Organization (WHO) group III with pulmonary htn associated with;
    - lung diseases and/or hypoxemia including chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitudes, developmental abnormalities
- Use in World Health Organization (WHO) group IV with pulmonary htn associated with:
    - chronic thrombotic and/or embolic disease including thromboembolic obstruction of proximal or distal pulmonary arteries
    - non-thrombotic pulmonary embolism (e.g. tumor, parasites, foreign material)
- Use in World Health Organization (WHO) group V with pulmonary htn associated with:
    - sarcoidosis, histiocytosisX, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)
- Left ventricular ejection fraction less than 45%
- Left ventricular shortening fraction less than 0.2

- Patients taking the below medications concurrently
    - alpha–adrenergic blocking agents (e.g. Uroxatral, Cardura, Minipress, Terazosin, Flomax). In some patients, concomitant use of these two drug classes can lower blood pressure significantly.
    - Anti-coagulants, since these agents inhibit platelet aggregation, there may be an increased risk of bleeding

NOTE : Abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage of these agents may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness and asthenia. In clinical trials, one Class III PPH patient's death was judged attributable to the interruption of FLOLAN. Abrupt withdrawal should be avoided.

Precautions

- *Hypotension* – These agents are pulmonary and systemic vasodilators. In patients with low systemic arterial pressure, treatment may produce symptomatic hypotension.
- Uptitrate slowly in patients with liver of renal insufficiency because of the risk of systemic exposure, this may lead to dose-dependent adverse effects. These agents metabolites are excreted through the urinary route, so decreased clearance may add to these side effects.
- *Risk of syncope* – Monitor vital signs while initiating Ventavis. Do not initiate Ventavis in patients with systolic blood pressure below 85 mmHg. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.
- *Bronchospasm* – The inhalant agents may produce bronchospasm that may be more severe or frequent in patients with a history of hyperreactive airways.

Pregnancy Risk Factor = B/C

There are no adequate and well controlled studies with treprostinil (Remodulin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri) in pregnant women. Because many drugs are excreted in human milk, caution should be exercised when administered to nursing women. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether treprostinil (Remodulin, Tyvaso), iloprost (Ventavis) and epoprostenol (Flolan, Veletri) is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision to discontinue nursing should be made, taking into account the importance of the drug to the mother.

Conditions of Coverage

Quantity Limitations	**treprostinil (Tyvaso)** – The maximum recommended dosage is 9 breaths (approximately 6 mcg per breath) per

	treatment session (54 mcg), 4 times daily. **treprostinil (Remodulin)** – The infusion rate should be increased in increments of 1.25 ng/kg/min per week for the first four weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. **iloprost (Ventavis)** – Starting dose: 2.5 mcg Uptitrate to 5 mcg if 2.5 mcg is well tolerated Maintenance dose: 5 mcg *Inhaled via the I-neb AAD System or the Prodose AAD Systen. Patient should received 6-9 doses (inhalations) per day with a minimum of 2 hours between doses during waking hours.* **epoprostenol (Flolan, Veletri)** – Initiate infusion at 2 ng/kg/min and increase in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted. If dose-limiting pharmacologic effects occur, then decrease the infusion rate until it is tolerated. The max dose is 16 ng/kg/min based upon patient weight, drug delivery rate, and concentration of the solution to be used. *Administered via continuous chronic infusion through a central venous catheter.*
J-Code	**J3285** - treprostinil (Remodulin) **J3490** - Iloprost (Ventavis) **J1325** - epoprostenol (Flolan, Veletri) **J7686** - treprostinil, inhalation solution (Tyvaso)
NDC	**Tyvaso** 66302020601 66302020602 66302020603 **Remodulin** 66302011001 66302010501 66302010201 66302010101 **Ventavis** 66215030330

	66215030230 **Flolan** 00173051900 00173051700 20694011101 20694011201 **Veletri** 66215040101 **Epoprostenol Sodium** 00703198501 00703199501
Applicable ICD-9 Codes	416.0 Pulmonary arterial hypertension 416.8 Other chronic pulmonary heart diseases (secondary pulmonary hypertension)
Place Of Service	Office, Outpatient, Home *****Preferred place of service is in the Home*** **Note:** CareSource supports administering inject able medications in various setting, as long as those services are furnished in the most appropriate and cost effective setting that are supportive of the patient's medical condition and unique needs and condition. The decision on the most appropriate setting for administration is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of the specific medication.
Authorization Period	Coverage may be approved for up to 12 weeks. Coverage may be approved for re-treatment if meeting initial diagnosis criteria and evidence of a beneficial response as shown by walking/exertion ability . Coverage depends on improvement in exercise capacity (6-minute walk test) versus baseline, improvement in NYHA class versus baseline, lack of deterioration.

D. REVIEW / REVISION HISTORY

06/15/2011

E. REFERENCES

Remodulin [package insert]. Research Triangle Park, NC: United Therapeutics Corp.: February 2011.

Tyvaso [package insert]. Research Triangle Park, NC: United Therapeutics Corp.

Ventavis [package insert]. South San Francisco, CA: Actelion Pharmacueticals US, Inc.: February 2011.

Flolan [package insert]. Research Triangle Park, NC: Glaxo smith Kline.: January 2008.

Veletri [package insert]. South San Francisco, CA: Actelion Pharmacueticals US, Inc.: September 2010.

Badesch DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: updated AACP evidence-based clinical practice guidelines. *Chest*. 2007;131:1917-1928.

McLaughlin, V.V.,MD & McGoon, M.D., MD, Pulmonary Arterial Hypertension. **Circulation. 2006;114:1417-1431.**

Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Introduction. Chest. 2004;126:7S-10S.

Hoeper MM, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Eng J Med 2000; 342:1866-70.

The medical Policy Statement detailed above has received due consideration as defined in the Medical Policy Statement Policy and is approved.

	June 13, 2011
Chief Medical Officer	**Date**
	June 13, 2011
Senior Medical Director	**Date**