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Medication Policy Manual

Policy No: dru337

Topic: Orenitram®, treprostinil oral tablets

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Next Review Date: April 2018

Effective Date: July 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Orenitram® (treprostinil oral) is an oral medication used in the treatment of pulmonary arterial hypertension (PAH).

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Policy/Criteria

I. Most contracts require prior authorization approval of treprostinil oral prior to coverage. Treprostinil oral may be considered medically necessary for treatment of pulmonary arterial hypertension (PAH) when criteria A, B, and C below are met:

A. There is a diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH) (See Appendix I).

AND

B. Treprostinil oral will be used as monotherapy.

AND

C. Sildenafil has been ineffective, not tolerated, or is contraindicated.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers treprostinil oral to be a self-administered medication.

B. When prior authorization is approved, treprostinil oral may be authorized in quantities not to exceed 42 mg per day.

C. Authorization of treprostinil oral may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Treprostinil oral is considered investigational when used for all other conditions, including but not limited to:

A. Use in combination with other PAH-specific medications, including epoprostenol injection (Flolan, Veletri), treprostinil inhaled (Tyvaso), treprostinil injection (Remodulin), iloprost (Ventavis), ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio), tadalafil (Adcirca) or riociguat (Adempas).

B. Pulmonary hypertension (PH) WHO Groups 2-5 (see Appendix II), including PH associated with:

1. Left heart disease, including congestive heart failure (CHF)
2. Lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)
3. Chronic thrombotic and/or embolic disease
4. Sarcoidosis

C. Digital ischemia and/or ulcers, including Raynaud's phenomenon, due to systemic sclerosis, scleroderma or other causes.

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Position Statement

- The World Health Organization (WHO) classifies pulmonary hypertension (PH) in five groups, based on underlying etiology of PH. [1]
    * Patients diagnosed with Group 1 pulmonary arterial hypertension (PAH) have generally irreversible disease and may require treatment with PAH-specific therapies.
    * For patients with Groups 2-5, PH may be reversible. Therapy should be directed at treating the underlying cause. [1,2]
- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin and prostacyclin analogs (PGEs) (epoprostenol, treprostinil, and iloprost), endothelin-receptor antagonists (ETAs) (ambrisentan, bosentan, macitentan), phosphodiesterase-5 inhibitors (PDE5s) (sildenafil, tadalafil) and riociguat, a soluble guanylate cyclase (sGC) stimulator.
- The place in therapy of individual agents for PAH is not well defined and is typically symptom driven. Generally, a step-wise approach is used to manage patients. In early disease or with less severe symptoms, oral therapies may be used. As symptoms progress, inhaled or injectable therapies, such as epoprostenol injection, iloprost inhaled and treprostinil injectable/inhaled, become necessary. [1]
- Treprostinil oral up to 12 mg twice daily has been shown to improve exercise tolerance in patients with pulmonary arterial hypertension (PAH) in the pivotal trial and up to 21 mg twice daily in the open-label extension trial. [3]
- The addition of treprostinil oral to other PAH-specific medications, such as oral PDE5s or ETAs, has not been shown not improve exercise tolerance over monotherapies. [3]
- For patients unable to tolerate twice daily dosing, treprostinil oral dosing may be divided in to three times per day dosing. [3]
- There are currently no trials of adequate design or of sufficient duration that demonstrate improved survival with treprostinil oral in patients with PAH.
- There insufficient evidence to establish any one oral therapy for PAH is clearly superior to another. Generic sildenafil is the lowest-cost oral medication for PAH and a treatment option for most treatment-naïve PAH patients.
- To date, there is no evidence that treprostinil oral is more effective than the other PAH-specific medications, as there are no comparative trials of treprostinil oral versus alternatives.
- There are currently no trials of treprostinil oral in patients with Groups 2-5 PH that found improvement in exercise capacity or overall functional status. Choosing Wisely®, an evidence-based initiative to promote wise use of medical resources, states that medications for PAH (e.g. PGEs, PDE5s, and ETAs) should not be used in patients with pulmonary hypertension due left heart disease or hypoxemic lung diseases (Groups 2 and 3), due to a lack of established benefit In addition, medications for PAH may be harmful in some situations and raises the overall cost of care. [4]

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Clinical Efficacy

- Treprostinil oral is used for the treatment pulmonary arterial hypertension (PAH) to improve exercise ability. [3] It was found to improve performance on the 6-minute walk test relative to placebo. The six-minute walk test (6MWD) is a measure of exercise tolerance and measures the distance that is covered in a 6-minute timeframe. Improvements in this test have been correlated to improved survival in PAH patients.
- In one low-confidence randomized, controlled study in adults with PAH: [5]
    * Treprostinil oral up to 12 mg twice daily modestly improved 6MWD compared to placebo. The mean dose at week 12 was 3.4±1.9 mg twice daily.
    * The trial was not powered for reduction of mortality, the most meaningful outcome for PAH.
    * This limited duration trial with a modest change in a surrogate endpoint provides little information about long-term treatment benefit.
    * The study was significantly flawed and was not able to be relied upon to make health care decisions. Flaws included a significant loss of the intent-to-treat population, moderately high attrition, differential loss and a protocol amendment post-randomization. Safety and efficacy results may be confounded.
    * There are no head-to-head studies of treprostinil oral versus other PAH therapies.
- Treprostinil oral has not been proven effective as add-on therapy to other PAH-specific medications. In two Phase 3 trials, addition of treprostinil oral did not significantly increase 6MWD in patients on a PDE5, ETA, or both (10 to 11 meters more than placebo). [6,7] A third combination therapy study protocol was withdrawn, prior to trial enrollment. [8]
- The safety and effectiveness of treprostinil oral has not been established in pediatrics. [3]
- There is no reliable evidence that doses of treprostinil oral exceeding 12 mg twice daily provide any additional clinical benefit when used in the treatment of PAH. [3]
- ACCP guidelines for treatment of pulmonary arterial hypertension recommend the use of an ERA, PDE-5, or riociguat for treatment-naïve PAH patients with WHO functional class (FC) II/III symptoms. Guidelines also recommend consideration of initial therapy with an injectable prostacyclin analog in WHO FC IV patients and select WHO FC III patients with rapid disease progression or poor prognostic markers. [9] Current guidelines do not include the use of treprostinil oral. [1,9]

Safety [3]

- Safety data for treprostinil oral is limited to adverse events described in the three clinical trials, as well as an extension trial of up to two years.
- Treprostinil oral has a safety profile similar to other PGEs. The most common adverse effects (≥ 10% more than placebo) include headache, diarrhea, and nausea.
- Like other PGEs, treprostinil oral inhibits platelets and increases the risk of bleeding. Use cautiously with anticoagulants, as well as antihypertensives or other vasodilators, due to potential for additive hypotension.

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Administration and Dosing [3]

- The recommended starting dose of treprostinil oral for the treatment of PAH 0.25 mg twice daily. Doses are titrated by 0.25 or 0.5 mg every three to four days as tolerated.
- Smaller dose increases of 0.125 mg, in dosed three times daily, may be used in patients not tolerating twice daily dose increases.
- There is no evidence to support the safety or efficacy of converting patients on injectable or inhaled PGE therapy to treprostinil oral. The FDA-approval of treprostinil oral was based on use in patients not on other PAH therapies. Conversion trials are ongoing. [8]

Use of Treprostinil Oral in Other Conditions

Other potential uses of treprostinil oral include the treatment of other types of pulmonary hypertension and other vasoconstrictive conditions, including digital ulcers related to Raynaud's phenomenon or systemic sclerosis.

- Guidelines do not support the use of bosentan for treatment of pulmonary hypertension (PH) in WHO Groups 2-5, including PH related to chronic left heart disease (WHO Group 2) or chronic hypoxic states (WHO Group 3). Instead, these patients require optimization of therapies targeting their underlying disease state. [1]
- Treprostinil oral is being studied in patients with digital ulcers and/or digital ischemia related to Raynaud's phenomenon, systemic sclerosis (SSc), or scleroderma, to improve peripheral blood flow and reduce digital ulcers. Results are not yet available. [8,10]

Cross References
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Letairis®, ambrisentan, Medication Policy Manual, dru219
Opsumit®, macitentan, Medication Policy Manual, dru324
Remodulin®, treprostinil injectable, Medication Policy Manual, dru222
Viagra®, Medication Policy Manual, dru117
tadalafil-containing medications, Cialis®, Adcirca®, Medication Policy Manual, dru184
Tyvaso®, treprostinil inhalation, Medication Policy Manual, dru221
Uptravi®, selexipag, Medication Policy Manual, dru446
Ventavis®, iloprost inhalation, Medication Policy Manual, dru220

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Appendix I: Revised World Health Organization (WHO) Classification of pulmonary hypertension (PH) – Group 1 [1]

Group 1. Pulmonary arterial hypertension (PAH)

- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH):*
    - Connective tissue disorder (e.g. rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, systemic sclerosis (formerly known as CREST syndrome)
    - Congenital systemic-to-pulmonary shunts (e.g. congenital heart disease (CHD), including atrial or ventricular septal defect, patent ductus arteriosus (PDA), patent foramen ovale (PFO), truncus arteriosus, Eisenmenger syndrome, tetralogy of Fallot, transposition of the great vessels)
    - Portal hypertension
    - HIV infection
    - Drugs and toxins (e.g. anorexic agents, cocaine, methamphetamine, L-tryptophan)
    - Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies (e.g. sickle cell anemia, thalassemia), chronic myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
    - Pulmonary veno-occlusive disease (PVOD)
    - Pulmonary capillary hemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn

* Diagnoses, include, but are not limited to these common diagnoses.

Appendix II: Investigational Indications for Sildenafil - Revised WHO Classification of PH – Groups 2-5 [1]

Group 2. Pulmonary hypertension with left heart disease

- Left-sided atrial or ventricular heart disease (systolic dysfunction, diastolic dysfunction)
- Left-sided valvular heart disease

Group 3. Pulmonary hypertension associated with lung diseases and/or hypoxemia

- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease (e.g. idiopathic pulmonary fibrosis)
- Sleep disordered breathing (e.g. obstructive sleep apnea (OSA))
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Group 5. Miscellaneous

- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

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Appendix III: Functional Status with Heart Failure

World Health Organization (WHO) functional assessment classification: [11]

Class I: Patients with pulmonary hypertension (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 physical activity.

New York Heart Association (NYHA) Heart Failure Classification: [12]

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Revision History

Revision Date	Revision Summary
6/9/2017	No changes to coverage criteria with this annual update.
6/10/2016	No changes

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