IMPORTANCE 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
Opsumit® (macitentan) is an oral medication used in the treatment of pulmonary arterial hypertension (PAH).
Policy/Criteria

I. Most contracts require prior authorization approval of macitentan prior to coverage. Macitentan may be considered medically necessary for treatment of pulmonary arterial hypertension (PAH) when criteria A and B below are met:
   A. There is a diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH) (See Appendix I).
   AND
   B. Sildenafil has been ineffective, not tolerated, or is contraindicated.

II. Administration, Quantity Limitations, and Authorization Period
   A. OmedaRx considers macitentan to be a self-administered medication.
   B. When prior authorization is approved, macitentan may be authorized in quantities of 30 tablets per month.
   C. Authorization of macitentan may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Macitentan is considered investigational when used for all other conditions, including but not limited to:
   A. Use in combination with treprostinil oral (Orenitram)
   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
      5. Systemic sclerosis with Raynaud's or digital ulcers.
   C. Raynaud's phenomenon, with or without digital ulcers

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 injectable, iloprost inhaled and treprostinil injectable/inhaled, become necessary. [1]

Macitentan 10 mg once daily has been shown to improve exercise tolerance in patients with pulmonary arterial hypertension (PAH). [3]

There are currently no trials of adequate design or of sufficient duration that demonstrate improved survival with macitentan 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.

ETAs have been studied individually in the treatment of PAH. To date, there is no evidence that any one of these products is more effective than the other.

There are currently no trials of ETAs 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]

Clinical Efficacy

Endothelin-receptor antagonists (ETAs) are used for the treatment pulmonary arterial hypertension (PAH) to improve exercise ability. [3,5,6] All three were 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 of macitentan in adults with PAH: [7]

Macitentan 10 mg once daily resulted in a 45% reduction in the occurrence of the primary endpoint compared to placebo. The primary composite endpoint was time to death, a significant morbidity event or worsening of PAH (symptoms or the need for additional treatment). Significant events were defined as atrial septostomy, lung transplantation, or initiation of injectable PGEs.
* The majority of the benefit was in reduction in percentage of patients with PAH clinical worsening (-12.8% placebo-subtracted), which includes measurement of 6MWD.

* Effect on the rate of death and need for PGE therapy was small (absolute difference -0.2% and -2%). The trial was not powered for reduction of mortality, the most meaningful outcome for PAH.

* The study was significantly flawed and was not able to be relied upon to make health care decisions. Flaws included assessment bias for morbidity events, moderately high attrition and inclusion of few patients from North America. [8]

* There are no head-to-head studies of macitentan with other PAH therapies. However, 64% of the patients in the pivotal trial continued on stable doses of PAH medications (61% PDE5s; 6% oral or inhaled PGEs). Macitentan has not been studied in combination with injectable PGEs [e.g. epoprostenol or treprostinil subcutaneous].

The safety and effectiveness of macitentan has not been established in pediatrics. [3]

There is no reliable evidence that doses of macitentan exceeding 10 mg daily provide any additional clinical benefit when used in the treatment of PAH. [3]

The use of ETAs, including macitentan, or PDE5s in combination with treprostinil oral is considered investigational. Treprostinil oral has not been proven effective as add-on therapy to other PAH-specific medications, including PDE5s or ETAs. 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). [9,10] A third combination therapy study protocol was withdrawn, prior to trial enrollment. [11]

ACCP guidelines for treatment of pulmonary arterial hypertension recommend the use of an ETA, PDE-5, or riociguat for treatment naïve PAH patients with WHO functional class (FC) II/III symptoms. The guidelines do not differentiate between medication options within each class. 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. [12] ACCF/AHA guidelines recommend the use of other endothelin receptor antagonists (bosentan and ambrisentan) in WHO Group 1 PAH (see Appendix I), based on systematic review of the literature, but do not include the use of macitentan. However, macitentan was not available at the time the guidelines were published.[1]

* Safety [3]

- Safety data for macitentan is limited to adverse events described in the one pivotal trial, of 101-118 weeks.

- The most frequent side effects (≥ 3% more than placebo) include anemia, nasopharyngitis/pharyngitis, bronchitis, headache, influenza, and urinary tract infection.
- The most concerning serious adverse effect (AE) with ERAs is potential for hepatotoxicity. Although the incidence of liver function test (LFT) abnormalities in clinical trials was low, macitentan has not been studied versus other ERAs; therefore, the relative risk of hepatotoxicity is unknown.

- Other serious class effects include worsening of pulmonary veno-occlusive disease (PVOD), fluid retention (peripheral edema), and decreased spermatogenesis.

- The use of bosentan, ambrisentan, and macitentan is limited by their risk for potential side effects and need to be weighed against the risk/benefit ratio in using other therapeutic alternatives.

- ERAs have a number of significant drug interactions with. Use of macitentan with strong CYP3A4 inducers or inhibitors should be avoided.

- Macitentan is a known teratogen and not for use in pregnant women. A restricted-distribution REMS program is in place, to ensure appropriate patient, provider and pharmacy education as well as the use of reliable contraception.

Administration and Dosing [3]
- The recommended dose of macitentan for the treatment of PAH 10 mg once daily.
- No additional benefit is observed above the recommended dose.

Use of Macitentan in Other Conditions
Other potential uses of macitentan include the treatment of other types of pulmonary hypertension and 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. [3]

- Macitentan is being studied in patients with Raynaud’s phenomenon and digital ulcers related to systemic sclerosis (SSc) to improve peripheral blood flow and reduce digital ulcers. Results are not yet available. [11]
Cross References

Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension, BlueCross BlueShield Association Medical Policy, 5.01.09, Issue 6.2016.

Adempas, riociguat, Medication Policy Manual, dru322

bosentan-containing medications, Tracleer®, Medication Policy Manual, dru218

Letairis®, ambrisentan, Medication Policy Manual dru219

Orenitram, treprostinil oral tablets, Medication Policy Manual, dru337

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

References


8. FDA Center for Drug Evaluation and Research. Approval package for Opsumit (macitentan) Tablets, application number NDA 204410; Medical Review. [cited 3/4/2016]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000TOC.cfm


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)
Appendix III: Functional Status with Heart Failure

World Health Organization (WHO) functional assessment classification: [13]

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: [14]

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

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