EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Inhaled Prostacyclin Products
- Ventavis® (iloprost inhalation solution – Actelion)
- Tyvaso® (treprostinil inhalation solution – United Therapeutics)

TAC APPROVAL DATE: 08/30/2017

OVERVIEW

Ventavis and Tyvaso are both inhaled prostacyclin vasodilators indicated for the treatment of pulmonary arterial hypertension (PAH).[1-2,8] Ventavis, which is given six to nine times per day, is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (based on New York Heart Association [NYHA] Class), and lack of deterioration. Studies establishing effectiveness involved mainly patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).[1] Tyvaso, which is given four times per day, is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability.[2] Studies establishing effectiveness mainly included those with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).[2] An updated treatment algorithm (2013) by the 2nd World Symposium on Pulmonary Hypertension (WSPH) states that patients with Functional Class II should be treated initially with oral therapies (e.g., Adempas® [riociguat tablets], sildenafil [Revatio®, generics {Note: brand name Revatio injection also available}], Adcirca® [tadalafil tablets], Opsumit® [macitentan tablets], Tracleer® [bosentan tablets], and Letairis® [ambrisentan tablets]).[7] Ventavis and Tyvaso are recommended for patients in Functional Class III and IV. In situations of inadequate response, combination therapy (including double or triple therapy) is recommended.

The WHO classification of functional capacity, which is an adaptation of the NYHA system, is in Table 1.[4] This provides a qualitative assessment of activity tolerance and is useful in monitoring disease progression and response to therapy.

Table 1. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.[4]

Class	Description
I	Patients in whom there is no limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

WHO – World Health Organization.

Pulmonary hypertension can be classified into five different groups.[3] Ventavis and Tyvaso are indicated in Group 1 PAH.[1-2] The five major categories of pulmonary hypertension are cited in Table 2.[6]

Table 2. Updated Classification of Pulmonary Hypertension.[6]

Group 1: Pulmonary Arterial Hypertension
Idiopathic
Heritable
BMPR2
ALK-1, ENG, SMAD9, CAV1, KCNK3
Unknown
Drug and toxin-induced
Associated with
Connective tissue disease
Human immunodeficiency virus infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Group 2: Pulmonary Hypertension Due to Left Heart Disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group 3: Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases
Group 4: Chronic Thromboembolic Pulmonary Hypertension
Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms
Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension.

BMPR2 – Bone morphogenic protein receptor type 2; ALK-1 – Activin-like receptor kinase-1; ENG – Endoglin; SMAD9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.

Guidelines

In 2004, the American College of Chest Physicians (ACCP) developed evidence-based clinical practice guidelines regarding the screening, early detection, and diagnosis of PAH.[4] In patients with suspected pulmonary hypertension, right heart catheterization is required to confirm the presence of pulmonary hypertension, establish the specific diagnosis, and determine disease severity (grade A recommendation). In patients with suspected pulmonary hypertension, right heart catheterization is required to guide therapy (grade B recommendation).[4] The 2007 ACCP guidelines for medical therapy for PAH also restate these recommendations.[5]

In 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[3] The guidelines state that the diagnosis of PAH requires confirmation with a complete right heart catheterization. The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ventavis and Tyvaso. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ventavis and Tyvaso as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ventavis and Tyvaso is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve for 3 years if the patient meets the following criteria (A, B, C and D):
   - **A)** The patient has a diagnosis of PAH (WHO Group 1); AND
   - **B)** The patient has had a right heart catheterization to confirm the diagnosis of PAH (WHO Group 1); AND
   - **C)** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
   - **D)** The patient meets ONE of the following criteria (i or ii):
     - **i.** The patient is in Functional Class III or IV; OR
     - **ii.** The patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:
       (1) The patient has tried or is currently receiving one oral agent for PAH (e.g., Tracleer [bosentan tablets], Letairis® [ambrisentan tablets], Opsumit® [macitentan tablets], Revatio®/Viagra® [sildenafil tablets], Adcirca®/Cialis® [tadalafil tablets]), Adempas® [riociguat tablets], Orenitram™ [treprostinil extended-release tablets], or Uptravi® [selexipag tablets]); OR
       The patient is unable to take any of the agents above (e.g., those with liver abnormalities [Tracleer], patient of childbearing potential [Tracleer, Letairis], concomitant use with nitrates [sildenafil, Adcirca/Cialis], hypotension, drug-drug interactions); OR
       (2) The patient has tried one inhaled or parenteral prostacyclin product for PAH (e.g., Tyvaso™ [treprostinil inhalation solution], Ventavis® [iloprost inhalation solution], Remodulin® [treprostinil injection], epoprostenol injection [Flolan®, Veletri®, generics]).

Ventavis and Tyvaso are both indicated for the treatment of PAH (WHO Group 1).[1-2] The clinical trials involving these products mainly included patients with NYHA Class III symptoms. The WSPH updated treatment algorithm for PAH (2013) recommends patients in Functional Class II should be treated with an oral agent for PAH (e.g., Tracleer, Opsumit, Letairis, Adempas, sildenafil, Adcirca).[7] Tyvaso and Ventavis are recommended in patients with Functional Class III and IV. ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend a right heart catheterization to confirm the presence of pulmonary hypertension, establish the diagnosis, and determine PAH disease severity.[4] An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, ATS and Pulmonary

Hypertension Association, note all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to the initiation of therapy.[3]

2. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1] for Patients Currently Receiving the Requested Inhaled Prostacyclin for PAH (i.e., Ventavis or Tyvaso) or Another Agent Indicated for WHO Group 1 PAH** (e.g., Adempas® [riociguat tablets], Viagra® [sildenafil tablets], Revatio® [sildenafil tablets and injection], Adcirca®/Cialis® [tadalafil tablets], Opsumit® [macitentan tablets], Tracleer® [bosentan tablets], Letairis® [ambrisentan tablets], Orenitram™ [treprostinil extended-release tablets], Uptravi® [selexipag tablets], Remodulin® [treprostinil injection], and epoprostenol injection [Flolan®, Veletri®, generics]). Approve for 3 years if the patient meets the following criteria (A and B):
   A) The patient has a diagnosis of PAH (WHO Group 1); AND
   B) The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

   The purpose of the criteria is to allow for continuation of therapy in patients who have not had a right heart catheterization or among those that do not have documentation of this procedure being performed.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ventavis and Tyvaso have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ventavis® inhalation solution [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc; November 2013.
2. Tyvaso® inhalation solution [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp.; June 2016.
3. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration with the American College of Chest Physicians: American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53:1573-1619.
4. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *CHEST*. 2004;126:14S-34S.
5. Badesch DB, Abman SH, Simonneau G. et al. Medical therapy for pulmonary arterial hypertension. *CHEST*. 2007;131:1917-1928. Available at: http://journal.publications.chestnet.org/data/Journals/CHEST/22057/1917.pdf. Accessed on June 8, 2014.
6. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41.
7. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D60-D72.
8. McLaughlin VV, Palevsky HI. Parenteral and inhaled prostanoid therapy in the treatment of pulmonary arterial hypertension. *Clin Chest Med*. 2013;34:825-840.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes.	08/05/2015
Annual revision	For patients with PAH (WHO Group 1), for patients currently receiving medication, Uptravi was added to the list of other PAH medications. For patients with Functional Class II, Uptravi was added as a medication option that counts towards the requirement to try one agent. Also, the phrase "women of childbearing potential" was changed to "patients of childbearing potential" in reference to exceptions to the requirement that one oral agent be tried first.	08/10/2016
Annual revision	No criteria changes.	08/30/2017

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; PAH – Pulmonary arterial hypertension; WHO – World Health Organization.