EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Phosphodiesterase type 5 (PDE5) Inhibitors

- Adcirca® (tadalafil tablets – Eli Lilly (Lung Biotechnology [a subsidiary of United Therapeutics])
- Revatio® (sildenafil tablets [generic], suspension and injection [generic] – Pfizer)

DATE REVIEWED: 08/30/2017

OVERVIEW

Revatio and Adcirca are phosphodiesterase type 5 (PDE5) inhibitors indicated for the treatment of pulmonary arterial hypertension (PAH).[1-2] Revatio is indicated for PAH (World Health Organization [WHO] Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol injection therapy (Flolan® [generic], Veletri®). Studies establishing its effectiveness were short-term (12 to 16 weeks) and included mainly patients with New York Heart Association (NYHA) Functional Class II to III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (25%).[1] A limitation of use is that adding Revatio to Tracleer® (bosentan tablets) does not result in any beneficial impact on exercise capacity. The recommended dose of Revatio is 5 mg or 20 mg three times daily (TID) given approximately 4 to 6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended. Revatio has a Warning regarding mortality with increasing doses in pediatric patients. In a long-term trial involving pediatric patients with PAH, an increase in mortality with increasing Revatio dose was noted. Deaths were first observed following about 1 year and causes of death were usual of those with PAH. Revatio, especially chronic use, is not recommended in children.[1] Adcirca is indicated for the treatment of PAH (WHO Group I) to improve exercise ability.[2] Studies establishing effectiveness were mainly in patients with NYHA Functional Class II to III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%). The recommended dose is 40 mg once daily (QD). Dividing the dose (40 mg) over the course of the day is not recommended.

Viagra® (sildenafil tablets) and Cialis® (tadalafil tablets) are indicated for the treatment of erectile dysfunction[3-4] and contain the same active ingredients as Revatio and Adcirca, respectively. Viagra is available in 25, 50, and 100 mg tablets.[3] Revatio is available as 20 mg tablets, as a powder for oral suspension (10 mg/mL strength when reconstituted), and as a 10 mg (12.5 mL) single use vial intended for intravenous (IV) infusion.[1] Revatio tablets (20 mg) are available generically. Cialis is available as 2.5, 5, 10, and 20 mg tablets.[4] Adcirca is available as 20 mg tablets.[2]

The WHO classification of functional capacity, which is an adaptation of the NYHA system, is in Table 1.[5] This provides a qualitative assessment of activity tolerance and is useful in monitoring disease progression and response to therapy.[5]

Table 1. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.[5]

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.[8] Adcirca and Revatio are indicated in Group 1 PAH.[1-2] The five major categories of pulmonary hypertension are cited in Table 2.[8]

Pulmonary hypertension can be classified into five different groups (categories), which are in Table 2.[8]

Table 2. Updated Classification of Pulmonary Hypertension.[8]

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 Hypoxemia
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.[5] 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).[5] The 2007 ACCP guidelines for medical therapy for PAH also restate these recommendations.[7]

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.[6] 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 Revatio and Adcirca. Because of the specialized skills required for evaluation and diagnosis of patients treated with Revatio and Adcirca as well as the monitoring required for adverse events (AEs) 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 Revatio tablets, Revatio suspension, Revatio injection, and Adcirca is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indication

A. Coverage of Revatio tablets, Revatio suspension, and Adcirca tablets is recommended in those who meet the following criteria:

1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve for 3 years if the patient meets the following criteria (A, B and C):
   - **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.

   Revatio is indicated for PAH (WHO Group I) to improve exercise ability and delay clinical worsening.[1] Adcirca is indicated for the treatment of PAH (WHO Group I) to improve exercise ability.[2] ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend to perform a right heart catheterization in patients with suspected pulmonary

hypertension to confirm the presence of pulmonary hypertension, establish the diagnosis, and to determine disease severity.[5,7] An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, ATS and Pulmonary Hypertension Association, notes all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to initiation of therapy.[6]

2. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1] for Patients Currently Receiving the Requested Phosphodiesterase Type 5 (PDE5) inhibitor (i.e., Revatio tablets, Revatio suspension or Adcirca) or Another Agent Indicated for WHO Group 1 PAH** (e.g., Adempas® [riociguat tablets], Viagra® [sildenafil tablets], Revatio injection, Cialis® [tadalafil tablets], Opsumit® [macitentan tablets], Tracleer® [bosentan tablets], Letairis® [ambrisentan tablets], Orenitram™ [treprostinil extended-release tablets], Uptravi® [selexipag tablets], Remodulin® [treprostinil injection], epoprostenol injection [Flolan®, Veletri®, generics], Ventavis® [iloprost inhalation solution], or Tyvaso® [treprostinil inhalation solution]). 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.

B. Coverage of Revatio injection is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].** Approve Revatio injection 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 is unable to take an oral PDE5 inhibitor (e.g., Revatio tablets, Adcirca, Viagra).

   Revatio is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening. Revatio injection is for the continued treatment of patients with PAH who are currently prescribed oral Revatio and who are temporarily unable to take oral medication.[1] ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend to perform a right heart catheterization in patients with suspected pulmonary hypertension to confirm the presence of pulmonary hypertension, establish the diagnosis, and to determine disease severity.[5,7] An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, ATS and Pulmonary Hypertension Association, notes all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to initiation of therapy.[6]

2. **Pulmonary Arterial Hypertension (WHO Group 1) for Patients Currently Receiving Revatio Injection or Another Agent Indicated for WHO Group 1 PAH** (e.g., Adempas, Revatio tablets, Revatio suspension, Viagra, Adcirca, Cialis, Opsumit, Tracleer, Letairis, Orenitram, Uptravi,

Remodulin, epoprostenol injection, Flolan, Veletri, Ventavis, or Tyvaso). Approve Revatio injection for 3 years if the patient meets the following criteria (A, B and C):

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; AND
C) The patient is unable to take an oral PDE5 inhibitor (e.g., Revatio tablets, Adcirca, Viagra).

Revatio is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening. Revatio injection is for the continued treatment of patients with PAH who are currently prescribed oral Revatio and who are temporarily unable to take oral medication.[1] 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

Revatio tablets, Revatio suspension, Revatio injection or Adcirca 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Erectile Dysfunction.** Coverage of Adcirca or Revatio is not recommended. Patients should use other PDE5 inhibitors indicated for erectile dysfunction.

2. 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. Revatio® tablets, oral suspension, and injection [prescribing information]. New York, NY: Pfizer; July 2017.
2. Adcirca® tablets [prescribing information]. Indianapolis, IN: Eli Lilly (marketed by lung Biotechnology, a subsidiary of United Therapeutics Corporation); August 2017.
3. Viagra® tablets [prescribing information]. New York, NY: Pfizer Labs; August 2017.
4. Cialis® tablets [prescribing information]. Indianapolis, IN: Eli Lilly; May 2017.
5. 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;126:14-34.
6. McLaughlin VV, Archer SL, Badesch DB, et al; Writing committee members. 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. *Circulation*. 2009;119:2250-2294.
7. Badesch, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension. Updated ACCP Evidence-based clinical practice guidelines. *CHEST*. 2007;131:1917-1928.
8. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Selected revision	Added that sildenafil injection is available as a generic.	Not applicable†
Annual revision	No criteria changes.	08/05/2015
Annual revision	For patients with pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1, for patients currently receiving therapy, Uptravi was added to the list of other PAH medications. Also, deleted the phrase "men with" regarding the diagnosis of erectile dysfunction, which is listed in the "Conditions Not Recommended for Approval" section.	08/10/2016
Annual revision	No criteria changes.	08/30/2017

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