EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Uptravi® (selexipag tablets – Actelion)

TAC APPROVAL DATE: 08/22/2018

OVERVIEW

Uptravi, a selective non-prostanoid IP prostacyclin receptor agonist, is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to delay disease progression and reduce the risk of hospitalization for PAH.[1] The efficacy of Uptravi was established in a long-term study in patients with PAH with mostly WHO functional class II to III symptoms. The recommended starting dose is 200 mcg twice daily (BID). Tolerability may be improved when taken with food. Increase the dose in increments of 200 mcg BID, usually at weekly intervals, to the highest tolerated dose up to 1,600 mcg BID. If treatment is missed for 3 days or more, restart Uptravi at a lower dose and then retitrate

Clinical Efficacy

The efficacy and safety of Uptravi was established in a multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase III, event-driven, published pivotal trial called GRIPHON that randomized adult patients with PAH (n = 1,156) to either placebo (n = 582) or Uptravi (n = 574) either as monotherapy or in combination with other PAH medications.[1-2] Most patients involved in the study (80%) were being treated with an endothelin receptor antagonist (ERA) as monotherapy (15%), a phosphodiesterase type 5 (PDE5) inhibitor as monotherapy (32%), or an ERA plus a PDE5 inhibitor in combination (33%).[1-2] The median duration of follow-up was approximately 67 weeks.[2] Uptravi resulted in a 40% reduction of the occurrence of primary endpoint events compared with placebo ($P < 0.0001$) which assessed death; hospitalization for PAH; PAH worsening [need for lung transplant or balloon atrial septostomy]; initiation of parenteral prostanoid therapy or chronic oxygen therapy; and other disease progression (e.g., need for added PAH therapy). Primary endpoint events were noted in 155 patients given Uptravi (27.0%) vs. 242 patients who received placebo (41.6%). At Week 26, the absolute change from baseline in the six minute walk distance (6MWD) [measured at trough] was +4 meters with Uptravi vs. -9 meters with placebo ($P = 0.005$).

The WHO classification of functional capacity, which is an adaptation of the New York Heart Association (NYHA) system, is in Table 1.[3] This provides a qualitative assessment of activity tolerance and is useful in monitoring disease progression and response to therapy in PAH.

Table 1. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.[3]

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 (categories), which are in Table 2.[4]

Table 2. Updated Classification of Pulmonary Hypertension.[4]

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 (CTEPH)
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/Recommendations

Guidelines or notable recommendations for the management of WHO Group 1 PAH have not addressed Orenitram® (treprostinil extended-release tablets) or Uptravi. In 2013, the 5th World Symposium on Pulmonary Hypertension (WSPH) discussed the treatment of PAH and published an updated treatment algorithm.[5] Regarding initial therapy for patients in WHO functional class II the following therapies were given a grade I recommendation (evidence level A or B): Letairis® (ambrisentan tablets), Tracleer® (bosentan tablets), Opsumit® (macitentan tablets), Adempas® (riociguat tablets), sildenafil and Adcirca® (tadalafil tablets). Grade 1 recommendations (evidence level A or B) for initial therapies for patients in WHO functional class III included the following: Letairis, Tracleer, Opsumit, Adempas, sildenafil, Adcirca, Ventavis® (iloprost inhalation solution), Tyvaso® (treprostinil inhalation solution), epoprostenol injection for intravenous use (Flolan®, Veletri®, generics) and Remodulin® (treprostinil injection for subcutaneous or intravenous use) administered subcutaneously. In WHO functional class III, Remodulin given intravenously was given a Grade IIa recommendation (evidence level C). In this population, initial combination therapy may

be utilized (ERAs ± PDE5 inhibitors/Adempas ± prostanoids). For WHO functional class IV, epoprostenol was given a Grade 1 recommendation (evidence level A or B). The following therapies were given a Grade IIa recommendation (level of evidence C): Letairis, Tracleer, Opsumit, Adempas, sildenafil, Adcirca, Ventavis, Tyvaso, and Remodulin (subcutaneous or intravenous). Initial combination therapy may be considered as well.

Information from the WSPH recommendations also note that many of the previously cited agents for PAH led to noted improvement when utilized in combination (using two or more classes of PAH medications simultaneously).[5] Additionally, other agents have shown improvement in outcomes such as the time to clinical worsening or improvements in WHO functional class. For example, the pivotal trial with Opsumit showed improvement in the composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of PAH compared with placebo long-term; benefits were noted both in patients who received background therapy and those who were receiving Opsumit monotherapy.[5] Opsumit is indicated for the treatment of PAH (WHO Group 1) to delay disease progression; the prescribing information notes that Opsumit also reduced hospitalization for PAH.[6] WSPH recommendations note that in a trial that studied the effects of adding sildenafil to epoprostenol injection, improvements after 12 weeks were noted regarding the 6MWD as well as in the time to clinical worsening.[5] Sildenafil (Revatio® formulation [tablets, suspension and injection {generics for tablets and injection}]) is indicated for patients with WHO Group 1 PAH to improve exercise ability and to delay clinical worsening.[7] The WSPH recommendations also state that in patients with PAH, Adempas has been shown to have favorable results not only regarding exercise capacity, but also in WHO functional class and time to clinical worsening.[5] Adempas is indicated in PAH to improve exercise capacity, improve WHO functional class and to delay clinical worsening.[8] In April 2013, the Agency for Healthcare Research and Quality published a document regarding the screening, management and treatment of PAH.[9] The document extensively details the robust clinical data that are available with the various medications utilized to treat patients with PAH and the benefits noted.

In 2004, the American College of Chest Physicians (ACCP) developed evidence-based clinical practice guidelines regarding the screening, early detection, and diagnosis of PAH.[10] 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).[3] The 2007 ACCP guidelines for medical therapy for PAH also restate these recommendations.[10]

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.[11] 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 Uptravi. Because of the specialized skills required for evaluation and diagnosis of patients treated with Uptravi as well as the

monitoring required for AEs and long-term efficacy, initial approval requires Uptravi 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.

Documentation: In the *Pulmonary Arterial Hypertension – Uptravi Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Uptravi Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Uptravi 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 the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 years if the patient meets the following criteria (i, ii, iii, and iv):
     - **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
     - **iii.** The patient meets the following criteria (a and b):
       - **a)** The patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** The results for the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iv.** The patient meets ONE the of following conditions (a or b):
       - **a)** The patient has tried two oral therapies for PAH (or is currently receiving them) from two of the three following different categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor (e.g., Revatio [sildenafil tablets], Adcirca [tadalafil tablets]), one endothelin receptor antagonist (ERA) [e.g., Tracleer, Letairis or Opsumit], or Adempas; OR
       - **b)** The patient is receiving, or has received in the past, one prostacyclin therapy for PAH (e.g., Orenitram, Tyvaso, Ventavis, Remodulin, or epoprostenol injection [Flolan, Veletri, generics]); OR
   - **B)** Patients Currently Receiving Uptravi. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):
     - **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
     - **iii.** The patient meets the following criteria (a and b):

a) The patient has had a right heart catheterization; AND
b) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH.

Uptravi is indicated for the treatment of PAH (WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH.[1] ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, and updated in 2007, 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.[3,10] 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.[11] Many therapies are available for PAH that have established benefits, either used alone or in combination.[5,9] Most patients in the pivotal trial with Uptravi were receiving other PAH background therapies.[1-2] Recommendations from the WSPH note that many medications are available for PAH that not only have more robust increases in exercise capacity, but some have also demonstrated improvement in clinical outcomes.[5] These criteria permit continuation of Uptravi therapy if patients have an established diagnosis of PAH WHO Group 1, have had appropriate diagnostic tests, and are being followed by, or have had consultation with, a specialist physician.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Uptravi has 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. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	Not applicable.	01/20/2016
Annual revision	No criteria changes.	02/08/2017
Annual revision	No criteria changes	02/14/2018
Annual revision	For initial review, documentation is required for the right heart catheterization. The criteria were deleted regarding patients "who are receiving another medication for WHO Group 1 PAH". For patients who are currently receiving Uptravi, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for patients who had previously provided documentation of the right heart catheterization upon coverage review for a different medication indicated for WHO Group 1 PAH, this documentation requirement is considered to be met.	08/22/2018

* 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.