BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 3/17/16**
SECTION: DRUGS	**LAST REVIEW DATE: 3/15/18**
	LAST CRITERIA REVISION DATE: 3/15/18
	ARCHIVE DATE:

UPTRAVI® (selexipag) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Description:

Uptravi (selexipag) is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to delay and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Pulmonary hypertension (PH) may be described by restricted or reduced blood flow through the pulmonary artery, pulmonary vein, or pulmonary capillaries, leading to complaints of shortness of breath, dizziness, fainting, fatigue, chest pain, palpitations, leg swelling and other symptoms. PH is a severe progressive disease with markedly decreased exercise tolerance, heart failure and ultimately death. The rate of progression is highly variable.

PH may be categorized, using the WHO scheme, into five classes or groups based on etiology and may be further characterized using the New York Heart Association (NYHA) Functional Class system modified for PH that is based on activity level and symptoms in an attempt to classify severity of disease clinically. It should be noted that while together all groups are called pulmonary hypertension, WHO Group 1 is called PAH and WHO Groups 2 through 5 are called PH. Other factors are used to determine an individual's risk category and assessment of prognosis. NYHA Functional Class I are those individuals least affected by their disease while those in Functional Class IV are most affected.

PAH is placed in WHO Group 1 and includes a large number of etiologies. It is important to distinguish PAH from other types of PH as PH from other causes is thought to differ pathophysiologically from PAH and may be managed differently.

The pathogenesis of PAH (WHO Group 1) is complex and incompletely understood; it is thought to involve an imbalance between vasoconstriction, vasodilation, and abnormal cellular proliferation. It includes genetic, inflammatory, and environmental factors that alter vascular structure and function in smooth muscle, endothelial cells, and adventitia. Included in this complexity are endothelial dysfunction (favoring vasoconstriction, thrombosis, and mitogenesis); increased levels of thromboxane A2, endothelin-1 (ET-1), and serotonin (5HT) which stimulate vasoconstriction, cell proliferation, and thrombosis; decreased levels of prostacyclin, nitric oxide, and vasoactive intestinal peptide (VIP) which favor vasoconstriction, cell proliferation, and thrombosis; and low levels of other mediators such as vascular endothelial growth factor (VGEF). VEGF is a signal protein that stimulates creation of new blood vessels which restore oxygen supply to tissues when blood flow is inadequate.

The pathogenesis of pulmonary hypertension from left heart disease (WHO Group 2) is completely different. There is no obstruction to blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood, causing pulmonary edema and pleural effusions. In hypoxic pulmonary hypertension (WHO Group 3), low levels of oxygen are thought to cause vasoconstriction of pulmonary arteries. In chronic thromboembolic pulmonary hypertension (CTEPH or WHO Group 4), the blood vessels are blocked or narrowed with blood clots. These last two groups also share some similar pathophysiology as seen in PAH (WHO Group 1).

A baseline assessment to determine PAH severity is performed before initiating therapy. Therapy should not be administered unless a diagnostic right heart catheterization (RHC) and extensive investigations for the etiology of PH have been performed. This assessment includes the following three key measures:

1. Functional impairment: This is determined by measuring exercising capacity and determining WHO or NYHA Functional Class.

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2. Hemodynamic derangement: The diagnosis of PH can be suspected based on echocardiography. However, a RHC is performed to accurately measure hemodynamic parameters and confirm PAH. Individuals with PAH typically undergo an invasive hemodynamic assessment and an acute vasoreactivity test before the initiation of advanced therapy. The hemodynamic definition of PAH is a mean pulmonary artery pressure greater than 25 mm Hg at rest. A pulmonary arterial wedge pressure or left ventricular end-diastolic pressure of less than 15 mm Hg is needed to exclude WHO Group 2 PH (due to left heart disease). PAH is also supported by increased pulmonary vascular resistance and transpulmonary gradient.

   Acute vasoreactivity test: The test involves administration of a short-acting vasodilator, then measuring hemodynamic response with a right heart catheter. An acute vasoreactivity test is considered positive if mean pulmonary artery pressure decreases by at least 10 mm Hg and to a value less than 40 mm Hg, with an increased or no change in cardiac output and a minimally reduced or no change in systemic blood pressure.

Definitions:

Pulmonary Hypertension Association (PHA)
The largest and oldest pulmonary hypertension (PH) association in the world. PHA is a community-based nonprofit support, education, advocacy and awareness association for PH.

Pulmonary Hypertension Care Centers (PHCC)
Center of Comprehensive Care (CCC):
A PHA accredited highly organized, full-time PH center that proficiently evaluates individuals with PH based on published evidence-based guidelines and provides expert treatment of individuals with PAH with all of the FDA-approved therapies. CCC also make important contributions to PH research and education.

Regional Clinical Program (RCP):
A PHA accredited center that proficiently evaluates individuals with PH based on published evidence-based guidelines and provides expert treatment of individuals with PAH with all non-parenteral therapies. A RCP must collaborate with its regional CCC by referring individuals that may benefit from opportunities unavailable at the RCP, including the initiation of advanced parenteral therapies and participation in clinical research protocols.

WHO Group, classification of Pulmonary Hypertension (PH)
- WHO Group 1 - Pulmonary arterial hypertension (PAH)
  - Idiopathic (IPAH)
  - Heritable / Familial
    - Activin receptor-like kinase (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia)
    - Bone Morphogenic Protein Receptor type II (BMPR)
    - Unknown
  - Drug- and toxin-induced
  - Associated with (APAH):

        - Congenital heart diseases – systemic to pulmonary shunts
        - Connective tissue disease
        - HIV infection
        - Portal hypertension
        - Schistosomiasis
    - Persistent pulmonary hypertension of the newborn
    - Associated with significant venous or capillary involvement
        - Pulmonary capillary hemangiomatosis (PCH)
        - Pulmonary veno-occlusive disease (PVOD)

- WHO Group 2 - Pulmonary hypertension owing to left heart disease
    - Left-sided arterial or ventricular heart disease
    - Left-sided valvular heart disease
    - Diastolic dysfunction
    - Systolic dysfunction

- WHO Group 3 - Pulmonary hypertension owing to lung disease and/or hypoxia
    - Alveolar hypoventilation disorders
    - Chronic exposure to high altitude
    - Chronic obstructive pulmonary disease
    - Developmental abnormalities
    - Interstitial lung disease
    - Other pulmonary diseases with mixed restrictive and obstructive pattern
    - Sleep-disordered breathing

- WHO Group 4 - Pulmonary hypertension due to Chronic thromboembolic pulmonary hypertension (CTEPH)
    - Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
    - Thromboembolic obstruction of distal pulmonary arteries
    - Thromboembolic obstruction of proximal pulmonary arteries

- WHO Group 5 - Pulmonary hypertension with unclear multifactorial mechanisms
    - Hematologic diseases: chronic hemolytic anemia (including sickle cell disease), myeloproliferative disease, splenectomy
    - Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid diseases
    - Systemic diseases: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
    - Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, compression of pulmonary vessels, Hemoglobinopathies, Hereditary hemorrhagic telangiectasia

WHO Functional Class (modified New York Heart Association (NYHA) for PH)

Functional Class I

No limitation in physical activity; ordinary physical activity does not cause dyspnea or fatigue, chest pain, or near syncope

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Functional Class II
Slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; comfortable with no symptoms at rest

Functional Class III
Marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; comfortable with no symptoms at rest

Functional Class IV
Unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity

Therapeutic classes of drugs used to treat pulmonary hypertension:

Calcium Channel Blockers – used only in a very select group of individuals
- Dihydropyridine class preferred

Endothelin receptor antagonists – bind to receptors in endothelium and vascular smooth muscle
- Ambrisentan (Letairis) – oral
- Bosentan (Tracleer) – oral
- Macitentan (Opsumit) – oral

Phosphodiesterase type 5 inhibitors – inhibit Phospodiesterase type-5 to increased cAMP
- Sildenafil (Revatio, and generics) – oral (generics available) and IV (available as brand Revatio)
- Tadalafil (Adcirca) – oral

Prostanoids – direct vasodilation of pulmonary & systemic arterial vascular beds, inhibit platelet aggregation
- Epoprostenol (Flolan, Veletri, generics) – continuous IV
- Iloprost (Ventavis) – inhaled delivery system
- Treprostinil
  - Orenitram ER – oral
  - Remodulin – can be SQ or IV
  - Tyvaso – inhaled delivery system

Soluble Guanylate Cyclase Stimulators – stimulate Nitric Oxide cGMP pathway to increase cGMP
- Riociguat (Adempas) – oral

Selective prostacyclin receptor (IP receptor) agonist
- Selexipag (Uptravi) – oral

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Uptravi (selexipag)

Medication class:
Prostacyclin; Prostacyclin IP Receptor Agonist; Vasodilator

FDA-approved indication(s):
- Treatment of pulmonary arterial hypertension (PAH, WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH
- Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms.

Recommended Dose:
- Initial dose: 200 mcg twice daily
    - Increase the dose in increments of 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1600 mcg twice daily

Maximum dosage
- 1,600 mcg twice daily

Available Dosage Forms:
- 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, & 1,600 mcg tablets
- Each strength is available as a bottle of 60 tablets
- The 200 mcg is also available as a bottle of 140 tablets
- Titration Pack has: bottle of 200 mcg with #140 tablets & bottle of 800 mcg with #60 tablets

Warnings, Precautions, and other Clinical Information:
- For patients with moderate hepatic impairment (Child-Pugh Class B), the starting dose should be 200 mcg once daily with titration using 200 mcg once daily at weekly intervals
- Avoid use in patients with severe hepatic impairment (Child-Pugh Class C)
- Discontinue if signs of pulmonary edema occur & consider the possibility of pulmonary veno-occlusive disease (PVOD)
- There is no information on use of Uptravi in individual on dialysis or in individual with glomerular filtration rates < 15 mL/min/1.73 m^2
- Woman who is breast feeding an infant or child should stop breast feeding
- The absolute bioavailability of selexipag is approximately 49%

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Criteria:

- **Criteria for initial therapy:** Uptravi (selexipag) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual is 18 years of age or older

2. Provider has advanced training in the management of pulmonary hypertension or is affiliated with a Pulmonary Hypertension Association (PHA) accredited Pulmonary Hypertension Care Center (PHCC)[1] at **ONE** of the following:
   - Center of Comprehensive Care (CCC)[1, 2]
   - Regional Clinical Program (RCP)[1, 2]
   - An equivalent center [2]

3. A confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with Functional Class II-III symptoms (WHO Group and Functional Class category must be submitted with request)

4. Right heart catheterization documents **ALL** of the following:
   - Mean pulmonary artery pressure > 25 mm Hg at rest
   - Pulmonary arterial wedge pressure ≤ to 15 mm Hg
   - Pulmonary vascular resistance > 3 Wood units

5. Vasoreactivity testing with negative results

6. Chronic lung diseases and other causes of hypoxemia are mild or absent

7. Venous thromboembolic disease is absent

8. Individual does not have other disorders, that would put them into WHO group 5 PH, including:
   - systemic disorders (e.g., sarcoidosis),
   - hematologic disorders (e.g., myeloproliferative diseases), and
   - metabolic disorders (e.g., glycogen storage disease)

9. Individual has failure, intolerance or contraindication to generic oral sildenafil

10. Individual has failure, intolerance or contraindication to **ONE** oral Endothelin Receptor Antagonist (ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit)] **OR** riociguat(Adempas))

11. There are **NO** contraindications.
    - Contraindications include:
      - Use with Gemfibrozil or other strong inhibitors of CYP2C8

[1] For a list of PHA-certified providers, go to www.phassociation.org/patients/findadoctor.
[2] If an individual has not been seen within 6 months but needs to continue therapy or begin initial therapy, a limited authorization will be given to allow sufficient time for the individual to be evaluated by a PHA-accredited provider affiliated with a CCC or RCP or by a provider with advanced training in the

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management of pulmonary hypertension at an equivalent center. Individuals in an active course of treatment will be allowed a 60-day transition of care period to permit ample time to consult with a PHA-certified or equivalent provider. The diagnosis of PAH must be confirmed by the PHA-certified or equivalent provider. Individuals with ongoing therapy must have an appointment with a CCC or RCP center or equivalent center at least yearly or more often as deemed clinically appropriate by the provider.

Initial approval duration:

- If the individual has **NOT** been seen by a PHA-certified or equivalent provider within 6 months **AND** the request is for initial **OR** continuation of therapy:
  - 60-day transition of care period to permit ample time to be seen by a PHA-certified or equivalent provider
- If seen by a PHA-certified or equivalent provider: 12 months

➢ **Criteria for continuation of coverage (renewal request):** Uptravi (selexipag) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a PHA-certified or equivalent provider at least yearly or more often as deemed clinically appropriate by the provider

2. The condition has not progressed or worsened while on therapy but remains at high risk
   - Benefit of therapy determined by reduced hospitalizations for PAH **OR** stabilization of 6-minute walking distance (6MWD) with no worsening of Functional Class symptoms

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section
   - Significant adverse effect such as:
     - Pulmonary veno-occlusive disease due to Uptravi

5. There are no significant interacting drugs

Renewal duration: If seen by a PHA-certified or equivalent provider: 12 months

Resources:

Uptravi. Package Insert. Revised by manufacturer 12/2017. Accessed 2-21-18.

Uptravi. Package Insert. Revised by manufacturer 12/2015. Accessed 2-21-17.

Uptravi. Package Insert. Reference ID ACT20151221b. Revised by manufacturer 12/2015. Accessed 12-29-2015.

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Taichman DB, Ornelas J, Chung L, et al.: Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults. CHEST Guideline and Expert Panel Report. 2014 Chest; 146(2):449-475.

Galie N, Humbert M, Vachiery JL, et al.: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology *ESC) and the European Respiratory Society (ERS). 2016 Eur Heart J; 37:67-119.

UpToDate: Classification and prognosis of pulmonary hypertension in adults. Current through Jan 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/classification-and-prognosis-of-pulmonary-hypertension-in-adults?search=pulmonary%20hypertension&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: Clinical feature and diagnosis of pulmonary hypertension in adults. Current through Jan 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-features-and-diagnosis-of-pulmonary-hypertension-in-adults?search=pulmonary%20hypertension&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

UpToDate: Treatment of pulmonary hypertension in adults. Current through Jan 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-pulmonary-hypertension-in-adults?search=pulmonary%20hypertension&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3#H5

Simmonneau G, Gatzoulis MA, Adatia I, et al.: Updated Clinical Classification of Pulmonary Hypertension. 2013 JACC; 62, 25 (Sup D): 34-41

Galie N, Corris PA, Frost A, et al.: Updated Treatment Algorithm of Pulmonary Arterial Hypertension. 2013 JACC; 62, 25 (Sup D): 60-72

Hansmann G, Apitz C. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016; 102: ii67–ii85

Krishnan U, Feinstein JA, Adatia I, et al.: Evaluation and Management of Pulmonary Hypertension in Children with Bronchopulmonary Dysplasia. 2017 J Pediatrics; 188:24-34

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.