Oral Pulmonary Arterial Hypertension Agents Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace, FocusRx and KeyRx formularies.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adcirca</strong> (tadalafil)&lt;sup&gt;a&lt;/sup&gt; Tablets</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*WHO Group I) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%)</td>
<td>40 mg (two 20 mg tablets) orally once daily; dividing the dose over the course of the day is not recommended</td>
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<tr>
<td><strong>Adempas</strong> (riociguat) Tablets</td>
<td>Treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (*WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class</td>
<td>1 mg orally three times daily. Initial doses may be started at 0.5 mg three times daily for those who may not tolerate the hypotensive effects. Up-titrated the dose by 0.5 mg three times daily according to blood pressure up to a maximum dose of 2.5 mg three times daily. Dose increases should be no sooner than 2 weeks apart.</td>
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<tr>
<td></td>
<td>Treatment of adults with pulmonary arterial hypertension (PAH), (*WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy was shown in patients on monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%)</td>
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<td>Agent(s)</td>
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<td>Dosage and Administration</td>
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| Letairis *(ambrisentan)* Tablets | Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1):  
• To improve exercise capacity and delay clinical worsening.  
• In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability |
| Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%) |
|                  | 5 mg orally once daily, with or without tadalafil 20mg once daily; At 4-week intervals, either the dose of Letairis or tadalafil can be increased, as needed and tolerated, to Letairis 10mg or tadalafil 40 mg. |
| Opsumit® *(macitentan)* Tablets | Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to reduce the risks of disease progression and hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%) |
|                  | 10 mg orally once daily. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended. |
| Orenitram *(treprostinil)* Tablets | Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to delay disease progression and to improve exercise capacity. The study that established effectiveness included predominately WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%). |
|                  | Starting dose is 0.25 mg orally twice daily 12 hours apart OR 0.125 mg three times daily taken approximately 8 hours apart.  
Titrate by 0.25 or 0.5 mg twice daily or 0.125 mg three times daily, not more than every 3-4 days as tolerated. Max dose based on tolerability. |
<table>
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<tr>
<th>Agent(s)</th>
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</thead>
<tbody>
<tr>
<td><strong>Revatio</strong>&lt;sup&gt;a&lt;/sup&gt; (sildenafil citrate)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*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 therapy. Studies establishing effectiveness were short-term (12 to 16 weeks) and included predominately patients with NYHA Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%). Limitation of use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.</td>
<td><strong>Oral tablets:</strong> 5 mg or 20 mg orally three times daily 4-6 hours apart; no greater efficacy seen with higher doses in clinical trial <strong>IV bolus injection:</strong> 2.5 mg or 10 mg IV bolus three times daily; IV injection is for patients temporarily unable to take oral medication <strong>Powder for oral suspension:</strong> 5 mg or 20 mg orally three times daily 4-6 hours apart; no greater efficacy seen with higher doses in clinical trial</td>
</tr>
<tr>
<td><strong>Tracleer®</strong> (bosentan) Tablets film coated&lt;sup&gt;a&lt;/sup&gt;, tablets soluble</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*WHO Group I): in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.</td>
<td><strong>Patients &gt;12 y.o. and &gt;40 kg:</strong> 62.5 mg orally twice daily for 4 weeks, then increase to 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of hepatotoxicity. <strong>Patients &gt;12 y.o. and &lt;40 kg:</strong> Initial and maintenance dose is 62.5 mg orally twice daily <strong>Patients ≤12 years of age and:</strong> ≥4-8 kg: 16 mg orally twice daily for both initial and maintenance dose &gt;8-16 kg: 32 mg orally twice daily for both initial and maintenance dose &gt;16-24 kg: 48 mg orally twice daily for both initial and maintenance dose &gt;24-40 kg: 64 mg orally twice daily for both initial and maintenance dose</td>
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<td>Agent(s)</td>
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<tr>
<td>Tyvaso® (treprostinil) Inhalation solution</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).  While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on background of bosentan (an endothelin receptor antagonist) or sildenafil (a PDE 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.</td>
<td>Administer in 4 separate treatment sessions each day approximately four hours apart, during waking hours.  Initial dosage: 3 breaths [18 mcg] inhaled per treatment session. If 3 breaths are not tolerated, reduce to 1 or 2 breaths.  Dosage should be increased by an additional 3 breaths per treatment session at approximately 1 to 2-week intervals, if tolerated.  Titrate to target maintenance dosage of 9 breaths (54 mcg) per treatment session as tolerated.  Max dose is 9 breaths per treatment session four times daily</td>
</tr>
<tr>
<td>Uptravi® (selexipag) Tablets</td>
<td>Treatment of pulmonary arterial hypertension (PAH, *WHO Group I) 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. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%)</td>
<td>Starting dose: 200 mcg orally twice daily.  Increase the dose by 200 mcg twice daily at weekly intervals to the highest tolerated dose up to 1600 mcg twice daily.</td>
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<td>Agent(s)</td>
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<tr>
<td><strong>Ventavis®</strong></td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%)</td>
<td>The first inhaled dose should be 2.5 mcg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 mcg and maintained at that dose; otherwise maintain the dose at 2.5 mcg. Ventavis should be taken 6 to 9 times per day (no more than once every 2 hours) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mcg (5 mcg 9 times per day).</td>
</tr>
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* - WHO = World Health Organization
a-generic available and included as a target.

**CLINICAL RATIONALE**

The World Health Organization (WHO) has classified pulmonary hypertension (PH) based upon etiology into the following five groups:¹⁵

- **Group 1** - Pulmonary arterial hypertension (PAH)
- **Group 2** – PH due to left heart disease
- **Group 3** – PH due to chronic lung disease and/or hypoxemia
- **Group 4** – PH due to chronic thromboembolic pulmonary hypertension
- **Group 5** – PH due to unclear multifactorial mechanisms

Group 1, also known as pulmonary arterial hypertension (PAH), is defined by a pre-capillary pattern in the invasive hemodynamic evaluation, characterized by a mPAP >20 mmHg with a normal pulmonary capillary wedge pressure (i.e., ≤15 mmHg) and a pulmonary vascular resistance ≥3 Wood units, in the absence of pulmonary parenchymal or thromboembolic disease. Group 1 can occur in isolation or in association with clinical conditions, as noted in the following subcategories: idiopathic, heritable, drug/toxin induced, association with other diseases (i.e., connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis), long-term responders to calcium channel blockers, with overt features of venous/capillaries (pulmonary veno-occlusive disease [PVOD]/pulmonary capillary haemangiomatosis [PCH]), and persistent PH of the newborn syndrome.¹⁵

Group 4 is due to chronic thrombotic and/or embolic disease including chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is characterized pathologically by organized thromboembolic material and altered by vascular remodeling initiated or potentiated by a combination of defective angiogenesis, impaired fibrinolysis and endothelial dysfunction. These changes lead to PH, defined as a mean pulmonary arterial pressure >20 mmHg, pulmonary capillary wedge pressure ≤15 mmHg, and pulmonary vascular resistance ≥3 Woods units. The hemodynamic changes occur in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least 3 months of effective anticoagulation. Ventilation/perfusion scan planar images combined with a confirmatory CT pulmonary angiography remain the preferred diagnostic tests for CTEPH despite advances in computed tomography (CT) and magnetic resonance (MR). CT and MR can be used in conjunction with the preferred diagnostic tests to identify complications of the disease but should not be solely relied upon due to concerns of false-positive cases mimicking CTEPH.¹²,¹⁷ The 6th World Symposium on Pulmonary Hypertension (WSPH)
recommends all patients diagnosed with CTEPH start with lifelong anticoagulation therapy. WSPH notes that antiplatelet therapy is not an alternative to anticoagulation in patients with CTEPH. Pulmonary endarterectomy (PEA) remains the first line treatment option for CTEPH. WSPH notes that the best treatment is uncertain for patients that may be technically operable but may not benefit from endarterectomy due to comorbidities. Targeted medical therapy is initiated in those patients that are inoperable or those with persistent/recurrent PH following PEA.

The diagnosis of PAH requires right heart catheterization (RHC) to demonstrate a mean pulmonary artery pressure >20 mmHg at rest and a pulmonary vascular resistance ≥3 Wood units. Several additional criteria to exclude the remaining categories of PH must also be met:14,15,19

- Mean pulmonary capillary wedge pressure ≤15 mmHg (to exclude PH due to left heart disease [i.e., group 2 PH])
- Chronic lung diseases and other causes of hypoxemia are mild or absent (to exclude PH owing to chronic lung disease or hypoxemia [i.e., group 3 PH])
- Venous thromboembolic disease is absent (to exclude chronic thromboembolic PH [i.e., group 4 PH])
- Certain miscellaneous disorders are absent, including systemic disorders (e.g., sarcoidosis), hematologic disorders (e.g., myeloproliferative diseases), and metabolic disorders (e.g., glycogen storage disease). The purpose is to exclude PH with unclear multifactorial mechanisms (group 5 PH).

World Health Organization (WHO) Functional Classification of Patients with Pulmonary Hypertension are:20

- Class I: Patients with PH without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or near syncope.
- Class II: Patients with PH having slight limitation of physical activity. No discomfort at rest, but ordinary physical activity causes increased dyspnea, fatigue, chest pain, or near syncope.
- Class III: Patients with PH having marked limitation of physical activity. No discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or near syncope.
- Class IV: Patients with PH unable to carry out any physical activity without symptoms and may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, with increased discomfort by any physical activity.

The 6th symposium on PAH also included recommendations for pediatric patients with PH. The 2019 guidelines and the 2015 American Heart Association and American Thoracic Society guidelines note that the definition of PAH in pediatric patients mirrors the adult definition. The guidelines also recommend the same diagnostic testing and algorithm as adult patients, with the inclusion of a full shunt evaluation during RHC to rule out congenital heart disease.13,18

Treatment Guidelines
Guidelines recommend that patients be referred to a PAH expert center for diagnosis confirmation and management. Current treatment strategies are based on the severity of newly diagnosed patients, assessed by a risk stratification approach. The risk stratification takes clinical, exercise, right ventricular function, and hemodynamic parameters, and combines them to define a low, intermediate, or high-risk status according to patients expected 1-year mortality. The risk stratification includes the following factors:11,13,14,20
### Determinates of prognosis (estimated 1-year mortality)

<table>
<thead>
<tr>
<th></th>
<th>Low Risk &lt;5%</th>
<th>Intermediate Risk 5-10%</th>
<th>High Risk &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Syncope</td>
<td>No</td>
<td>Occasional during brisk or heavy exercise, or occasional orthostatic in an otherwise stable patient</td>
<td>Repeated with little or regular physical activity</td>
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<tr>
<td>WHO functional class</td>
<td>I-II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>6-minute walking distance</td>
<td>&gt;440 meters</td>
<td>165-440 meters</td>
<td>&lt;165 meters</td>
</tr>
<tr>
<td>Cardiopulmonary exercise testing</td>
<td>Peak VO$_2$ &gt;15 ml/min/kg (&gt;65% pred.) VE/VCO$_2$ slope &lt;36</td>
<td>Peak VO$_2$ 11-15 ml/min/kg (35-65% pred.) VE/VCO$_2$ slope 36–44.9</td>
<td>Peak VO$_2$ &lt;11 ml/min/kg (&lt;35% pred.) VE/VCO$_2$ slope ≥45</td>
</tr>
<tr>
<td>N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels</td>
<td>BNP &lt;50 ng/l NT-proBNP &lt;300 ng/l</td>
<td>BNP 50–300 ng/l NT-proBNP 300–1400 ng/l</td>
<td>BNP &gt;300 ng/l NT-proBNP &gt;1400 ng/l</td>
</tr>
<tr>
<td>Imaging (echocardiography, CMR imaging)</td>
<td>RA area &lt;18 cm$^2$ No pericardial effusion</td>
<td>RA area 18–26 cm$^2$ No or minimal, pericardial effusion</td>
<td>RA area &gt;26 cm$^2$ Pericardial effusion</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;8 mmHg CI ≥2.5 L/min/m$^2$ SvO$_2$ &gt;65%</td>
<td>RAP 8–14 mmHg CI 2.0–2.4 L/min/m$^2$ SvO$_2$ 60–65%</td>
<td>RAP &gt;14 mmHg CI &lt;2.0 L/min/m$^2$ SvO$_2$ &lt;60%</td>
</tr>
</tbody>
</table>

BNP: brain natriuretic peptide; CI: cardiac index; CMR: cardiac magnetic resonance; pred.: predicted; RA: right atrium; RAP: right atrial pressure; SvO$_2$: mixed venous oxygen saturation; VE/VCO$_2$: ventilatory equivalents for carbon dioxide; VO$_2$: oxygen consumption

The 6th World Symposium on Pulmonary Hypertension evidence-based treatment algorithm for adults:\textsuperscript{11,16}

- **Treatment Naïve patients:**
  - Head-to-head comparisons among different compounds are not available, no evidence-based first line treatment can be proposed for initial monotherapy, if monotherapy is chosen.
  - Vasoreactive patients (only idiopathic PAH, heritable PAH, or drug induced PAH):
    - High dose calcium channel blockers (CCB) that have been progressively titrated
    - Response should be evaluated after 3 to 6 months
    - Adequate treatment response is defined as WHO-FC I/II with sustained hemodynamic improvement after at least 1 year on CCBs alone
    - Patients without an adequate response to high dose CCBs should be treated with approved PAH medications according to non-vasoreactive treatment strategy
  - Non-vasoreactive patients:
Low or intermediate risk: Treat with initial oral combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type-5 (PDE5) inhibitor (listed in sequence by recommendation rating)

- WHO-FC II: ambrisentan plus tadalafil, or other ERA and PDE5 combination
- WHO-FC III: ambrisentan plus tadalafil, or other ERA and PDE5 combination

High risk: Initial combination therapy (an ERA and a PDE5 inhibitor) plus IV prostacyclin (listed in sequence by recommendation rating)

- WHO-FC III/IV: bosentan plus sildenafil plus IV epoprostenol, bosentan plus IV epoprostenol, other ERA/PDE5 plus SC treprostinil, other ERA/PDE5 plus other IV prostacyclin

Response should be evaluated after 3 to 6 months:

- Low risk at follow up: continue therapy with structured follow up until risk progression
- Intermediate risk: Triple sequential combination therapy or double combination therapy in case initial monotherapy was chosen (listed in sequence by recommendation rating and alphabetical order)
  - WHO-FC II: macitentan added to sildenafil, riociguat added to bosentan, selexipag added to ERA and/or PDE5, treprostinil inhaled added to sildenafil or bosentan, iloprost inhaled added to bosentan, tadalafil added to bosentan, ambrisentan added to sildenafil, bosentan added to sildenafil, other double combinations, other triple combinations
  - WHO-FC III/IV: macitentan added to sildenafil, riociguat added to bosentan, selexipag added to ERA and/or PDE5, sildenafil added to epoprostenol, treprostinil inhaled added to sildenafil or bosentan, iloprost inhaled added to bosentan, tadalafil added to bosentan, ambrisentan added to sildenafil, bosentan added to epoprostenol, bosentan added to sildenafil, other double combinations, other triple combinations
- Macitentan plus sildenafil, riociguat plus bosentan, selexipag plus ERA and/or PDE5 have the highest levels of recommendations and evidence
- Referral for lung transplant should also be considered

- High risk: maximal medical therapy including an IV prostacyclin is recommended and listing for lung transplant
  - bosentan plus sildenafil plus IV epoprostenol, bosentan plus IV epoprostenol, other ERA/PDE5 plus SC treprostinil, other ERA/PDE5 plus other IV prostacyclin

- If still at intermediate or high risk after second treatment step (3 to 6 months after change in therapy), maximal medical therapy (triple therapy including a SC or IV prostacyclin [IV preferred for high risk]) is recommended and listing for lung transplant
  - Intermediate-risk status on double combination therapy with an ERA and a PDE5 or riociguat, the addition of selexipag should be considered
  - Triple combination therapy including selexipag who remain in the intermediate-risk group or progress to high risk, substitution with SC or IV prostacyclin should be considered

- Transitioning patients from one PAH-specific therapy to another might be considered for a number of reasons, but transitioning patients that have an extraordinary response to therapy and desire to transition to less invasive therapy is not recommended except in rare circumstances and under close expert care

The 6th World Symposium on Pulmonary Hypertension pragmatic treatment algorithm in pediatrics:11,18
• Treatment with targeted PAH therapies in children is almost exclusively based on experience and data from adult studies, due to the lack of pediatric clinical trials
• Patients with a positive vasoreactive response should be initiated on oral CCBs and continued if there is sustained and improved response.
• Recommend vasoreactive patients remain on CCBs in addition to targeted PAH therapies
• Non-vasoreactive patients or those with failed or non-sustained response should undergo risk stratification to determine therapy. Pediatric risk stratification is as follows:

<table>
<thead>
<tr>
<th>Determinates of Risk</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of right heart failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6-minute walking distance (&gt;6 years of age)</td>
<td>&gt;350 meters</td>
<td>&lt;350 meters</td>
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<tr>
<td>Growth</td>
<td>Normal</td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>WHO functional class</td>
<td>I, II</td>
<td>III, IV</td>
</tr>
<tr>
<td>N-terminal pro-brain natriuretic peptide plasma levels</td>
<td>Minimally elevated</td>
<td>Significantly elevated, Rising level</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>NA</td>
<td>RA/RV enlargement</td>
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<tr>
<td></td>
<td></td>
<td>Reduced LV size</td>
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<td></td>
<td></td>
<td>Increased RV/LV ratio</td>
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<td></td>
<td></td>
<td>Reduced TAPSE</td>
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<tr>
<td></td>
<td></td>
<td>Low RV FAC</td>
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<tr>
<td></td>
<td></td>
<td>Pericardial effusion</td>
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<tr>
<td>Hemodynamics</td>
<td>Systemic CI &gt;3.0 L/min/m² Systemic venous saturation &gt;65% Acute vasoreactivity</td>
<td>Systemic CI &lt;2.5 L/min/m² mRAP &gt;10 mmHg PVRI &gt;20 WU/m² Systemic venous saturation &lt;60% PACI &lt;0.85 ml/mmHg/m²</td>
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</table>

RV: right ventricle; WHO: World Health Organization; RA: right atrium; LV: left ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; CI: cardiac index; mRAP: mean right atrial pressure; PVRI: pulmonary vascular resistance index; WU: Wood Units; PACI: pulmonary arterial compliance index.

- Low risk: oral monotherapy with either an ERA (i.e., bosentan, ambrisentan) or a PDE5 inhibitor (i.e., sildenafil, tadalafil) is recommended
- Early combination therapy should be considered in children that deteriorate on either ERA or PDE5 therapy
  - Remain low risk despite deterioration: addition of inhaled prostacyclin may be beneficial
- High risk: IV epoprostenol or treprostinil are recommended, with early consideration of lung transplantation in patients with deteriorating high-risk features

The American College of Chest Physicians (CHEST) guidelines (2019) state:
• WHO FC II [treatment naive and not a candidate for or failure to calcium channel blocker (CCB) therapy]:
  - Combination with ambrisentan and tadalafil
Patients unable to tolerate or unwilling to take combination therapy:
monotherapy with an ERA or PDE5 inhibitor (listed in order of recommendation level and alphabetically)
  ▪ Ambrisentan, sildenafil, bosentan, macitentan, tadalafil, riociguat
Parenteral or inhaled prostanoids should not be used as initial or second line therapy
  • WHO FC III [treatment naïve, not a candidate for or failure to calcium channel blocker (CCB) therapy, and no evidence of rapid progression of their disease or poor prognosis]:
    ▪ Combination with ambrisentan and tadalafil
  • WHO FC III [treatment naïve with evidence of rapid progression of their disease, or other markers of a poor clinical prognosis]:
    ▪ Initial treatment with IV or SC prostanoid
    ▪ Suggest the addition of an inhaled prostanoid (i.e., treprostinil, iloprost) in patients that remain symptomatic on stable and appropriate doses of an ERA or PDE5 inhibitor
    ▪ There is no recommendation for patients unwilling to manage PAH with IV or SC prostanoid, so may consider addition of an inhaled or oral prostanoid,
  • WHO FC III [who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents]: addition of a parenteral or inhaled prostanoid
  • WHO FC IV [treatment naïve]: monotherapy with a parenteral prostanoid agent
  • WHO FC IV [treatment naïve and unable/or do not desire parenteral prostanoid therapy]: an inhaled prostanoid in combination with an ERA or PDE5 inhibitor
  • WHO FC III or IV [with unacceptable or deteriorating clinical status despite established PAH pharmacotherapy]: a second or third class of PAH therapy should be started
  ▪ Due to insufficient evidence, recommendations cannot be made for or against the use of selexipag
  ▪ There is no evidence to support the use of oral treprostinil as add-on or combination therapy

The AHA/ATS guidelines for the treatment of pediatric pulmonary hypertension state\textsuperscript{16}:
  • Oral therapy in children with lower-risk PAH is recommended and should include either a PDE5 inhibitor or an ERA
  • A goal-targeted therapy approach in which PAH-specific drugs are added progressively to achieve specified therapeutic targets can be useful
  • Intravenous and subcutaneous prostacyclin or its analogs should be initiated without delay for patients with higher-risk PAH

The Chest guidelines recognize that there is still a lack of head-to-head comparisons of pharmacologic agents for the treatment of PAH, and because of their differing burdens and risks to patients, it is recommended that drug therapy be chosen on the basis of a methodical evaluation of disease severity and the risk for further short-term deterioration. The optimal method of evaluation has not been studied. No one agent can be definitively recommended preferentially. Additionally, it notes that adding a second class of PAH therapy for patients whose clinical status remains unacceptable despite established PAH-specific monotherapy requires that the clinician assess whether the patient has received an adequate trial of the initial monotherapy. At present, this assessment combines evaluation of the duration of monotherapy, the expected response to the monotherapy, the observed response to the monotherapy, and the patient’s severity of illness and pace of decline. Unacceptable clinical
status will vary for individual patients and clinicians, but symptomatic limitation of desired physical activities usually guides these decisions.\textsuperscript{20}

**Safety**

Adcirca\textsuperscript{2}

Tadalafil has the following contraindications:
- Concurrent use (regular or intermittent) of organic nitrates in any form
- Do not use Adcirca in patients who are using a Guanylate Cyclase (GC) stimulator, such as riociguat
- History of known serious hypersensitivity reaction to tadalafil (Adcirca or Cialis)

Adempas\textsuperscript{6}

Riociguat has the following contraindications:
- Pregnancy
- Co-administration with nitrates or nitric oxide donors (e.g., amyl nitrite) in any form
- Concomitant use with specific phosphodiesterase (PDE) inhibitors (e.g., sildenafil, tadalafil, vardenafil) or nonspecific PDE inhibitors (e.g., dipyridamole, theophylline)
- Pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP)

Black box warnings include:
- Do not administer Adempas to a pregnant female because it may cause fetal harm. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Females of reproductive potential: exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment.

Letairis\textsuperscript{3}

Ambrisentan has the following contraindications:
- Pregnancy
- Idiopathic pulmonary fibrosis (including IPF patients with pulmonary hypertension [WHO group 3])

Black box warnings include:
- Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment.

Opsumit\textsuperscript{5}

Macitentan has the following contraindication:
- Pregnancy

Black box warnings include:
- Do not administer Opsumit to a pregnant female because it may cause fetal harm. Opsumit was consistently shown to have teratogenic effects when administered to
animals. If Opsumit is used during pregnancy, advise the patient of the potential risk to a fetus.

- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

**Orenitram**
Treprostinil tablets have the following contraindication:
- Severe hepatic impairment (Child-Pugh Class C)

**Revatio**
Sildenafil has the following contraindications:
- Concomitant use of organic nitrates in any form, either regularly or intermittently
- Concomitant use of riociguat
- Known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension

**Tracleer**
Bosentan has the following contraindications:
- Pregnancy
- Use with cyclosporine A
- Use with glyburide
- Hypersensitivity to bosentan or any component of the product

Black box warnings include:

*Hepatotoxicity*
In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly.

In the post marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy with Tracleer in patients with multiple comorbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded. In at least one case, the initial presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by nonspecific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction.

Elevations in aminotransferases require close attention. Tracleer should generally be avoided in patients with elevated aminotransferases (>3 × ULN) at baseline because monitoring for hepatotoxicity may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥2 × ULN, treatment with Tracleer should be stopped. There is no experience with the reintroduction of Tracleer in these circumstances.

*Embryo-Fetal Toxicity*
Tracleer is likely to cause major birth defects if used by pregnant females based on animal data. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of reproductive potential must use two reliable methods of contraception unless the patient has an intrauterine device (IUD) or tubal sterilization, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective.

**Uptravi**

Selexipag has the following contraindication:

- Concomitant use of a strong CYP2C8 inhibitor (e.g., gemfibrozil)

**REFERENCES**


# Oral Pulmonary Arterial Hypertension Agents Prior Authorization with Quantity Limit

## TARGET AGENTS
- Adcirca (tadalafil)
- Adempas (riociguat)
- Letairis (ambrisentan)
- Opsumit® (macitentan)
- Orenitram® (treprostinil)
- Revatio (sildenafil)
- Tracleer® (bosentan)
- Tyvaso® (treprostinil)
- Uptravi® (selexipag)
- Ventavis® (iloprost)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI (NDC)</th>
<th>Multisource Code</th>
<th>Quantity Per Day Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adcirca (tadalafil)</td>
<td>40143080000320</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>Adempas (riociguat)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mg tablet</td>
<td>4013405000****</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
</tr>
<tr>
<td>1 mg tablet</td>
<td>4013405000****</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
</tr>
<tr>
<td>1.5 mg tablet</td>
<td>4013405000****</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
</tr>
<tr>
<td>2.0 mg tablet</td>
<td>4013405000****</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
</tr>
<tr>
<td>2.5 mg tablet</td>
<td>4013405000****</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
</tr>
<tr>
<td>Letairis (ambrisentan)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg tablet</td>
<td>4016000700****</td>
<td>M, N, O, or Y</td>
<td>1 tablet</td>
</tr>
<tr>
<td>10 mg tablet</td>
<td>4016000700****</td>
<td>M, N, O, or Y</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Opsumit (macitentan)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg tablet</td>
<td>4016005000****</td>
<td>M, N, O, or Y</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Orenitram (treprostinil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.125 mg tablet</td>
<td>4017008005****</td>
<td>M, N, O, or Y</td>
<td>N/A</td>
</tr>
<tr>
<td>0.25 mg tablet</td>
<td>4017008005****</td>
<td>M, N, O, or Y</td>
<td>N/A</td>
</tr>
<tr>
<td>1 mg tablet</td>
<td>4017008005****</td>
<td>M, N, O, or Y</td>
<td>N/A</td>
</tr>
<tr>
<td>2.5 mg tablet</td>
<td>4017008005****</td>
<td>M, N, O, or Y</td>
<td>N/A</td>
</tr>
<tr>
<td>5 mg tablet</td>
<td>4017008005****</td>
<td>M, N, O, or Y</td>
<td>N/A</td>
</tr>
<tr>
<td>Revatio (sildenafil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg tablet</td>
<td>40143060100320</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
</tr>
<tr>
<td>10 mg/mL oral suspension</td>
<td>40143060101920</td>
<td>M, N, O, or Y</td>
<td>2 bottles (224 mL)/30 days</td>
</tr>
<tr>
<td>Tracleer (bosentan)</td>
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</tr>
<tr>
<td>32 mg tablet</td>
<td>40160015007320</td>
<td>M, N, O, or Y</td>
<td>4 tablets</td>
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<tr>
<td>62.5 mg tablet</td>
<td>40160015000320</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>125 mg tablet</td>
<td>40160015000330</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>Tyvaso (treprostinil)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 mg/mL System Starter Kit inhalation solution</td>
<td>40170080002020 (66302-206-01)</td>
<td>M, N, O, or Y</td>
<td>1 kit/180 days</td>
</tr>
<tr>
<td>0.6 mg/mL System Refill kit inhalation solution</td>
<td>40170080002020 (66302-206-02)</td>
<td>M, N, O, or Y</td>
<td>1 package of 28 ampules/28 days</td>
</tr>
</tbody>
</table>

a- generic available, subject to prior authorization with quantity limit
**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

**Initial Evaluation**

**Target Agent(s)** will be approved when ALL of the following are met:

1. ONE of the following:
   a. BOTH of the following:
      i. Information has been provided that indicates the patient is currently being treated with the requested agent in the past 90 days OR
      ii. The prescriber states that the patient is currently being treated with the requested agent in the past 90 days AND is at risk if therapy is changed
   AND
   b. The patient has an FDA labeled indication for the requested agent OR
   c. The patient has a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), WHO Group 4 and ALL of the following:
      i. The requested agent is Adempas
      AND
      ii. The patient’s diagnosis has been confirmed by a ventilation-perfusion scan and a confirmatory selective pulmonary angiography
      AND
      iii. The patient has a mean pulmonary artery pressure of >20 mmHg
      AND
      iv. The patient has a pulmonary capillary wedge pressure ≤15 mmHg
      AND
      v. The patient has a pulmonary vascular resistance ≥3 Wood units
      AND
      vi. One of the following:

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### 0.6 mg/mL 4 pack inhalation solution
- **40170080002020**
- **M, N, O, or Y**
- 7 packages of 4 ampules/28 days

### Institutional starter kit inhalation solution
- **40170080002020**
- **M, N, O, or Y**
- 1 kit/180 days

### Uptravi (selexipag)

<table>
<thead>
<tr>
<th>Item</th>
<th>Code</th>
<th>Patient Numbers</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titration pack</td>
<td>4012007000B720</td>
<td>M, N, O, or Y</td>
<td>1 pack/180 days</td>
</tr>
<tr>
<td>200 mcg tablet</td>
<td>4012007000310 (66215-0602-06)</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>Titration Bottle 200 mcg tablet</td>
<td>4012007000310 (66215-0602-14)</td>
<td>M, N, O, or Y</td>
<td>140 tablets/180 days</td>
</tr>
<tr>
<td>400 mcg tablet</td>
<td>4012007000315</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>600 mcg tablet</td>
<td>4012007000320</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>800 mcg tablet</td>
<td>4012007000325</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>1000 mcg tablet</td>
<td>4012007000330</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>1200 mcg tablet</td>
<td>4012007000335</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>1400 mcg tablet</td>
<td>4012007000340</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>1600 mcg tablet</td>
<td>4012007000345</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>

### Ventavis (iloprost)

<table>
<thead>
<tr>
<th>Item</th>
<th>Code</th>
<th>Patient Numbers</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mcg/mL inhalation solution</td>
<td>40170060002020</td>
<td>M, N, O, or Y</td>
<td>9 packages of 30 ampules/30 days</td>
</tr>
<tr>
<td>20 mcg/mL inhalation solution</td>
<td>40170060002040</td>
<td>M, N, O, or Y</td>
<td>9 packages of 30 ampules/30 days</td>
</tr>
</tbody>
</table>

---

*a - generic available, subject to prior authorization with quantity limit*
1. The patient is NOT a candidate for surgery
   OR
2. The patient has had a pulmonary endarterectomy AND has persistent or recurrent disease
   AND
   vii. The patient will NOT be using the requested agent in combination with a PDE5 inhibitor (e.g., tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra])
   OR
   c. The patient has a diagnosis of pulmonary arterial hypertension (PAH), WHO Group 1 and ALL of the following:
      i. The patient’s diagnosis has been confirmed by right heart catheterization
      AND
      ii. The patient’s mean pulmonary arterial pressure is >20 mmHg
      AND
      iii. The patient has a pulmonary capillary wedge pressure ≤15 mmHg
      AND
      iv. The patient has a pulmonary vascular resistance ≥3 Wood units
      AND
      v. The patient’s World Health Organization (WHO) functional class is II or greater
      AND
      vi. If the requested agent is Adcirca, Adempas, Revatio, sildenafil, or tadalafil, the patient will NOT be using the requested agent in combination with a PDE5 inhibitor (e.g., tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra])
      AND
      vii. ONE of the following:
         1. The request is for Adcirca (tadalafil) for use in combination with Letairis (ambrisentan) for dual therapy ONLY
         OR
         2. The requested agent will be utilized as monotherapy
         OR
         3. The requested agent will be utilized for add-on therapy to existing monotherapy (dual-therapy) [except combo requests for Adcirca with Letairis for dual therapy], and BOTH of following:
            a. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy
            AND
            b. The requested agent is in a different therapeutic class
            OR
         4. The requested agent will be utilized for add-on therapy to existing dual therapy (triple therapy) and ALL of the following:
            a. The patient is WHO functional class III or IV
            AND
            b. ONE of the following:
               i. A prostanoid has been started as one of the agents in the triple therapy
               OR
               ii. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL prostanoids
               AND
               c. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy
               AND
d. All three agents in the triple therapy are from a different therapeutic class

AND

viii. If the requested agent is a brand product with a generic equivalent, then ONE of the following:

1. The patient’s medication history includes the required generic equivalent as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days OR
   b. The prescriber has stated that the patient has tried the generic equivalent in the past 999 days AND the generic equivalent was discontinued due to lack of effectiveness or an adverse event

OR

2. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent

OR

3. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent
   OR
   a. The patient is currently being treated with the requested agent as indicated by ALL of the following:
      i. A statement by the prescriber that the patient is currently taking the requested agent AND
      ii. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent AND
      iii. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

4. The prescriber has provided documentation that the generic equivalent cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

   OR
   d. The patient has another FDA approved diagnosis for the requested agent
   AND

2. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., cardiologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis

AND

3. The patient does not have any FDA labeled contraindications to the requested agent

AND

4. For all agents except Orenitram, ONE of the following:
   a. The requested quantity (dose) does NOT exceed the program quantity limit
   OR
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit AND
      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

**OR**

c. ALL of the following:
   i. The requested quantity (dose) is greater than the program quantity limit
   AND
   ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
   AND
   iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

**Length of Approval:** 12 months

**Renewal Evaluation**

**Target Agent(s)** will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s Prior Authorization process
   AND
2. The patient has had clinical benefit with the requested agent
   AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., cardiologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis
   AND
4. The patient does not have any FDA labeled contraindications to the requested agent
   AND
5. For all agents except Orenitram, ONE of the following:
   a. The requested quantity (dose) does NOT exceed the program quantity limit
   **OR**
   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
      AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
   **OR**
   c. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
      AND
      ii. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication
      AND
      iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

**Length of Approval:** 12 months