<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adcirca</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 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>
</tr>
<tr>
<td>Adempas</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. 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>
<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-titrate 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>
</tr>
<tr>
<td>Letairis</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1): To improve exercise capacity and delay clinical worsening.</td>
<td>5 mg orally once daily, with or without tadalafil 20mg once daily; At 4-week intervals, either the dose of Letairis or tadalafil...</td>
</tr>
<tr>
<td>Agent(s)</td>
<td>Indication</td>
<td>Dosage and Administration</td>
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<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Opsumit® (macitentan) Tablets</td>
<td>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%).</td>
<td>10 mg orally once daily. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended.</td>
</tr>
<tr>
<td>Orenitram (treprostinil) Tablets</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.</td>
<td>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.</td>
</tr>
<tr>
<td>Revatio (sildenafil citrate) Tablets, oral solution, injection solution</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) 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%).</td>
<td>Oral tablets: 5 mg or 20 mg orally three times daily 4-6 hours apart; no greater efficacy seen with higher doses in clinical trial IV bolus injection: 2.5 mg or 10 mg IV bolus three times daily; IV injection is for patients temporarily unable to take oral medication Powder for oral suspension: 5 mg or 20 mg orally three times daily 4-6 hours apart; no greater</td>
</tr>
<tr>
<td>Agent(s)</td>
<td>Indication</td>
<td>Dosage and Administration</td>
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<tr>
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</tbody>
</table>
| **Tracleer®** (bosentan) | **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. | Patients >12 y.o. and >40 kg:  
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.  
Patients >12 y.o. and <40 kg:  
Initial and maintenance dose is 62.5 mg orally twice daily  
Patients ≤12 years of age and ≥4-8 kg: 16 mg orally twice daily for both initial and maintenance dose  
>8-16 kg: 32 mg orally twice daily for both initial and maintenance dose  
>16-24 kg: 48 mg orally twice daily for both initial and maintenance dose  
>24-40 kg: 64 mg orally twice daily for both initial and maintenance dose |
| **Tyvaso®** (treprostinil) | **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%).** | 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 1-2 week intervals, if tolerated.  
Titrate to target maintenance dosage of 9 breaths (54 mcg) per treatment session as tolerated. |

Tablets film coated, tablets soluble

Inhalation solution
<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uptravi®</strong></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>Max dose is 9 breaths per treatment session four times daily. 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>
</tr>
<tr>
<td>(selexipag)</td>
<td>Tablets</td>
<td></td>
</tr>
<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>
<tr>
<td>(iloprost)</td>
<td>Inhalation solution</td>
<td></td>
</tr>
</tbody>
</table>

* - WHO = World Health Organization

**CLINICAL RATIONALE**

The World Health Organization (WHO) has classified pulmonary hypertension (PH) based upon etiology into the following five groups:¹⁻⁹

- 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 ≥25 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, and association with other diseases (i.e., connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis).¹⁻²⁰
Group 4 is due to chronic thrombotic and/or embolic disease including chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is defined as mean pulmonary arterial pressure ≥25 mmHg and pulmonary capillary wedge pressure ≤15 mmHg 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. CTEPH is traditionally treated with surgery. Pulmonary endarterectomy is the treatment of choice and the only potential for cure for symptomatic, operable, CTEPH patients. Surgery however, is not an option for all patients and some patients who have undergone surgery have persistent or recurrent pulmonary hypertension.

The diagnosis of PAH requires right heart catheterization (RHC) to demonstrate a mean pulmonary artery pressure ≥25 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:

- 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 Functional Classification of Patients with Pulmonary Hypertension are:

- 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 mild 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 at rest and may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, with increased discomfort by physical activity.

The 5th symposium on PAH also included recommendations for pediatric patients with PH. The 2013 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.

**Treatment Guidelines**

Therapy for pulmonary arterial hypertension (PAH) includes drugs for anticoagulation, for decreasing pulmonary vascular resistance, for underlying disease, and for right ventricular failure. Vasodilators that have been found effective include calcium channel blockers (e.g., high dose diltiazem, nifedipine), and prostacyclin (e.g., epoprostenol, treprostinil). Endothelin
receptor antagonists (ERA) and phosphodiesterase type 5 (PDE-5) inhibitors have been shown to increase exercise tolerance.11

The 5th World Symposium on Pulmonary Hypertension evidence-based treatment algorithm for adults:12,18

- Head-to-head comparisons among different compounds are not available, no evidence-based first line treatment can be proposed for either WHO-FC II or III patients.
- WHO-FC I: These patients do not require pharmacologic therapy; however, they should be monitored closely for disease progression to a functional level that may warrant therapy.
- WHO-FC II: Either an ERA (it is noted that macitentan has morbidity and mortality as the primary endpoint in RCT; however, they do not prefer one over the other), a PDE5 inhibitor, or riociguat.
- WHO-FC III: Any of the following can be used – An ERA, A PDE5 inhibitor, epoprostenol, iloprost (inhaled), riociguat, or treprostinil subcutaneous or inhaled (it is noted that epoprostenol IV and macitentan have morbidity and mortality as primary endpoint in RCT or reduction in all-cause mortality (prospectively defined); however, none are preferred over the other).
- WHO-FC IV: Epoprostenol improves symptoms, exercise capacity, and hemodynamics in both clinical conditions, and is the only treatment shown to reduce mortality in idiopathic PAH in a RCT. Continuous IV epoprostenol is recommended as first-line therapy for WHO-FC IV PAH patients because of the survival benefit in this subset. In absence of IV epoprostenol all other compounds may be utilized. In these patients initial combination therapy may also be considered.
- In case of inadequate clinical response, sequential combination therapy should be considered. Combination therapy can either include an ERA + PDE5 inhibitor or a prostanoid plus and ERA or a prostanoid plus a PDE5 inhibitor. Riociguat can be considered as a potential alternative to PDE inhibitor in the different types of double combinations. The combination of riociguat and PDE5 inhibitors is contraindicated.
- In case of inadequate clinical response with double combination therapy, triple combination therapy should be attempted.

The 5th World Symposium on Pulmonary Hypertension evidence-based treatment algorithm in pediatrics:23

- In pediatric patients, risk stratification should determine therapy. Pediatric determinants of high risk include: clinical evidence of right ventricular failure, progression of symptoms, syncope, failure to thrive, WHO FC III or WHO FC IV, significantly elevated or rising B-type natriuretic peptide levels, severe right ventricular enlargement or dysfunction, and pericardial effusion.
- Hemodynamic parameters that predict higher risk include a PAPm to systemic artery pressure ratio >0.75, right atrial pressure >10 mmHg, and PVRI >20 Wood units x m².
- Low risk patients (WHO FC I-II): oral monotherapy with an ERA or PDE5.
- High risk patients (WHO FC III-IV): IV epoprostenol or treprostinil, or early consideration for combination with an ERA or PDE5.
- Deterioration on either ERA or PDE5 may benefit from early combination therapy, with an inhaled prostacyclin for low risk patients.

The American College of Chest Physicians (CHEST) guidelines (2014) state11:

- WHO FC II [treatment naïve and not a candidate for or failure to calcium channel blocker (CCB) therapy]: monotherapy with an endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE5) inhibitor, or riociguat
- WHO FC III [treatment naïve and not a candidate for or failure to calcium channel blocker (CCB) therapy]: monotherapy with an ETRA, a PDE5 inhibitor, or riociguat
• WHO FC III treatment naïve with evidence of rapid progression of their disease, or other markers of a poor clinical prognosis: initial treatment with a parenteral 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 ETRA.
• WHO FC III or IV with unacceptable or deteriorating clinical status despite established PAH pharmacotherapy, a third class of PAH therapy should be started.

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 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of pulmonary hypertension state that if a patient is vasoreactive, a CCB should be given as first line. Non-responders to acute vasoreactivity testing can be treated with either initial monotherapy or combination therapy. The choice of drug depends on approval status, labeling, route of administration, side-effect profile, potential interaction with background therapies, patient preference, co-morbidities, physician experience and cost. Since a head-to-head comparison between initial combination therapy with ambrisentan plus tadalafil has proven superior to initial monotherapy with either agent alone in delaying clinical failure, a higher grade of recommendation has been given to this initial combination. In non-vasoreactive and treatment-naïve patients at high risk, initial combination therapy including IV prostacyclin analogues should be considered. IV epoprostenol should be prioritized since it has reduced the 3-month rate of mortality in high-risk PAH patients. In case of inadequate clinical response with sequential double combination therapy, triple combination therapy should be attempted.\textsuperscript{13,14}

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{11}

For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, the guideline advises an addition of a second class of PAH therapy to improve exercise capacity. Such patients are ideally evaluated at centers with expertise in the
evaluation and treatment of complex patients with PAH. Data from RCTs are not available to inform the addition of a third pharmacologic class of PAH medication. However, addition of a third class of PAH medication usually indicates poor functional status. In this setting, the guidelines state that treatment with a parenteral prostanoid therapy must be considered.1

The recommendations for combination therapy should be used as general guidelines until more is known about which combinations are most efficacious and the optimal timing of combining therapies is available. Until then, an individualized approach should be used by a practitioner who has experience using combination therapy for PAH. In general, escalation of therapy and referral for lung transplantation evaluation should occur when a patient has evidence of disease progression on combination therapy.1

Safety

Adcirca2

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)

Adempas6

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 by using effective forms of contraception.

Letairis3

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**
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 (>20 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 (PAH) Agents Prior Authorization with Quantity Limit

**TARGET AGENTS**
- Adcirca (tadalafil)<sup>a</sup>
- Adempas (riociguat)
- Letairis (ambrisentan)<sup>a</sup>
- Opsumit® (macitentan)
- Orenitram® (treprostinil)
- Revatio (sildenafil)<sup>a</sup>
- Tracleer® (bosentan)<sup>a</sup>
- Tyvaso® (treprostinil)
- Uptravi® (selexipag)
- Ventavis® (iloprost)

<sup>a</sup>- generic available, subject to prior authorization with quantity limit

<table>
<thead>
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<th>Brand (generic)</th>
<th>GPI (NDC)</th>
<th>Multisource Code</th>
<th>Quantity Per Day Limit</th>
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<td>Adcirca (tadalafil)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>40143080000320</td>
<td>M, N, O, or Y</td>
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<td>Adempas (riociguat)</td>
<td>4013405000****</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
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<td>4013405000****</td>
<td>M, N, O, or Y</td>
<td>3 tablets</td>
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<td>M, N, O, or Y</td>
<td>3 tablets</td>
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<tr>
<td>Letairis (ambrisentan)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>401600700****</td>
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<td>1 tablet</td>
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<td>Revatio (sildenafil)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>40143060101920</td>
<td>M, N, O, or Y</td>
<td>2 bottles (224 mL)/30 days</td>
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<td>Tracleer (bosentan)</td>
<td>40160015007320</td>
<td>M, N, O, or Y</td>
<td>4 tablets</td>
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<td>40160015000320</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
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<td>4016001500330</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
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<tr>
<td>Tyvaso (treprostinil)</td>
<td>40170080002020</td>
<td>M, N, O, or Y</td>
<td>1 kit/180 days</td>
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<td>M, N, O, or Y</td>
<td>1 package of 28 ampules/28 days</td>
</tr>
<tr>
<td>206-02) inhalation solution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
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<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>0.6 mg/mL 4 pack</td>
<td>40170080002020</td>
<td>M, N, O, or Y</td>
<td>7 packages of 4 ampules/28 days</td>
</tr>
<tr>
<td>Carton- (66302-206-03) inhalation solution</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Institutional starter kit (66302-206-04) inhalation solution</td>
<td>40170080002020</td>
<td>M, N, O, or Y</td>
<td>1 kit/180 days</td>
</tr>
</tbody>
</table>

**Uptravi (selexipag)**

<table>
<thead>
<tr>
<th>Titration pack</th>
<th>4012007000B720</th>
<th>M, N, O, or Y</th>
<th>1 pack/180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mcg tablet</td>
<td>4012007000310</td>
<td>M, N, O, or Y</td>
<td>2 tablets</td>
</tr>
<tr>
<td>(66215-0602-06)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Titration Bottle</td>
<td>4012007000310</td>
<td>M, N, O, or Y</td>
<td>140 tablets/180 days</td>
</tr>
<tr>
<td>200 mcg tablet</td>
<td>(66215-0602-14)</td>
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<td></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>
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**Ventavis (iloprost)**

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<thead>
<tr>
<th>10 mcg/mL inhalation solution</th>
<th>40170060002020</th>
<th>M, N, O, or Y</th>
<th>9 packages of 30 ampules/30 days</th>
</tr>
</thead>
<tbody>
<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>
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</table>

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

Initial Evaluation

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

1. **ONE** of the following:
   a. **BOTH** of the following:
      i. There is documentation that the patient is currently being treated with the requested agent **OR** the prescriber states that the patient is currently being treated with the requested agent **AND** is at risk if therapy is changed
      **AND**
      ii. The patient has an FDA labeled indication for the requested agent
   **OR**
   b. If Adempas, then **ONE** of the following:
      i. The patient has a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), WHO Group 4, as determined by a ventilation-perfusion scan and a confirmatory selective pulmonary angiography and **ALL** of the following:
         1. The patient has both a mean pulmonary artery pressure of \( \geq 25 \) mmHg and a pulmonary capillary wedge pressure \( \leq 15 \) mmHg
         **AND**
         2. **ONE** of the following:
            a. The patient is **NOT** a candidate for surgery **OR**

a - generic available, subject to prior authorization with quantity limit
b. The patient has had a pulmonary endarterectomy AND has persistent or recurrent disease

OR

ii. The patient has a diagnosis of pulmonary arterial hypertension (PAH), WHO Group 1 as determined by right heart catheterization and ALL of the following:

1. The patient’s mean pulmonary arterial pressure is ≥ 25 mmHg AND
2. The patient has a pulmonary vascular resistance > 3 Wood units AND
3. The patient’s World Health Organization (WHO) functional class is II or greater AND
4. The patient will not be taking an PDE5 inhibitor (e.g. tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra]) at the same time as the requested agent AND
5. ONE of the following:
   a. The requested agent will be utilized as monotherapy
   OR
   b. The requested agent will be utilized for add-on therapy to existing monotherapy (dual-therapy) and BOTH of the following:
      i. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy AND
      ii. The requested agent is in a different therapeutic class
   OR
   c. The requested agent will be utilized for add-on therapy to existing dual therapy (triple therapy) and ALL of the following:
      i. The patient is WHO functional class III or IV AND
      ii. A prostanoid has been started as one of the agents in the triple therapy unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a prostanoid AND
      iii. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy AND
      iv. All three agents in the triple therapy are from a different therapeutic class

OR

iii. The patient has another FDA labeled diagnosis for the requested agent

OR

c. If Adcirca, Letairis, Opsumit, Orenitram, Revatio, sildenafil, tadalafil, Tracleer, Tyvaso, Uptravi, or Ventavis, the patient has a diagnosis of pulmonary arterial hypertension (PAH), WHO Group 1 as determined by right heart catheterization and ALL of the following:

i. The patient’s mean pulmonary arterial pressure is ≥ 25 mmHg AND
ii. The patient has a pulmonary vascular resistance > 3 Wood units
iii. The patient’s World Health Organization (WHO) functional class is II or greater

iv. If Adcirca, Orenitram, Revatio, sildenafil, or tadalafil the patient will not be taking another PDE5 inhibitor (e.g., tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra]) at the same time as the requested agent

v. 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 a documented intolerance, FDA labeled contraindication, or hypersensitivity to a prostanoid

         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

vi. If the request is for the brand Adcirca or Revatio then ONE of the following:
   1. The patient’s medication history includes use of the generic prerequisite agent (e.g., sildenafil, tadalafil)

   OR

   2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the generic prerequisite agent (e.g., sildenafil, tadalafil) that is not expected to occur with the requested agent

   OR

   3. The prescriber has submitted documentation supporting the use of the requested brand agent

   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
      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 submitted documentation 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 for renewal when the following met:
1. The patient has been previously approved for the requested agent through the Prime Therapeutics 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 submitted documentation in support of therapy with a higher dose for the requested indication

**Length of Approval:** 12 months
Non-Preferred Drug with Continuation of Therapy Prior Authorization Program Summary

This program applies to Medicaid.

APPLICATION
These criteria apply to non-preferred drugs listed in the Minnesota Medicaid Preferred Drug List (PDL). These criteria apply only to FDA approved legend drugs which are covered under the member’s current benefit plan. Medications which are investigational or otherwise not a covered benefit should be forwarded for review under the appropriate process.

Non-Preferred Drug Prior Authorization Criteria

February 2019

Approval criteria:
A request for coverage of a non-preferred drug may be approved if the following criteria are met:

• The drug is not excluded from coverage (e.g., drugs for weight loss, drugs for erectile dysfunction are excluded from coverage); AND

• The drug is prescribed for a medically accepted indication as defined in Sec. 1927 of the Social Security Act; AND

• The member has been taking the requested non-preferred drug to treat a mental illness or emotional disturbance as defined by Minnesota Statute 62Q.527 for at least 90 days; OR

• The requested drug is being prescribed within recommended dosing guidelines; AND

• The member has had a trial of at least two preferred chemically unique drugs within the same drug class on the Preferred Drug List, or a trial of at least one preferred drug within the same drug class if there are not two chemically unique preferred drugs within the same drug class; AND

• The prescriber must provide documentation (e.g., pharmacy dispensing record, medication orders in members’ health record, etc.) at the time of request that:
  o the member was adherent to the previous therapies during the trial(s) AND
  o the trial was sufficient period of time sufficient to allow for a positive treatment outcome, or that the drug was discontinued due to an adverse event; OR

• The member is currently taking the requested non-preferred drug and is experiencing a positive therapeutic outcome AND the prescriber provides documentation that switching the member to a preferred drug is expected to cause harm to the member or that the preferred drug would be ineffective; OR

• The preferred drug is contraindicated pursuant to the pharmaceutical manufacturer's prescribing information or, due to a documented adverse event or medical condition, is likely to result in the following:
  o cause an adverse reaction, OR
  o decrease the ability of the member to achieve or maintain reasonable functional ability in performing daily activities; OR
  o cause physical or mental harm to the member.

Duration of Approval
• Up to 12 months

**Quantity limits**

• Quantity limits pursuant to the FDA-approved label will apply

**Note**

• If applicable, the non-preferred drug prior authorization criteria does not bypass a clinical prior authorization for a specific drug.

**Continuation of Therapy Prior Authorization Criteria**

February 2019

**Definition:**

**Biosimilar Substitution:** Dispensing a biosimilar product rather than the reference biologic product.

**Cash Pay:** Allowing a member to pay for the entire cost of a non-covered prescription, after a member, in consultation with the prescriber and the pharmacist, has decided that covered alternatives are not options. A member may pay for the entire cost of a non-covered controlled substance prescription, including gabapentin, only when the member meets all conditions specified in the Advanced Recipient Notice of Non-Covered Prescription Form (DHS-3641-ENG)

**Continuation of Therapy:** Allowing a member who has been stabilized on a medication that requires prior authorization, but was previously covered by another payer (i.e., commercial insurance, MCO Medicaid plans), to continue the therapy without the prescriber having to satisfy the Fee-for-Service prior authorization criteria.

**Free goods/pharmaceutical samples:** medication samples, medications obtained from any patient assistance programs, medications obtained through free trial programs, manufacturer vouchers, coupons or debit cards.

**Generic Substitution:** Dispensing a generically equivalent drug rather than the brand name drug.

**Continuation of Therapy criteria:**

Continuation of Therapy override may be approved for non-preferred or restricted drugs if the following conditions are met:

• The requested non preferred or restricted drugs are not excluded from coverage (e.g., drugs for weight loss, drugs for erectile dysfunction); AND

• The requested non-preferred or restricted drugs are prescribed for a medically accepted indication as defined in Sec. 1927 of the Social Security Act, AND

• The member has been treated with a non-preferred or restricted drugs at a consistent dosage for at least 90 days and the prescriber indicates (orally or in writing) that the prescribed medication will best treat the member’s condition; AND

• The pharmacy or prescriber must provide an attestation that the medication was covered by another payer and not obtained via cash pay, drug manufacturer-issued debit cards, or via free goods/pharmaceutical samples.
Continuation of Therapy may be approved for the following duration:
- Continuation of Therapy override may be approved for up to 90 days. After 90 days, the prescriber must obtain prior authorization for the non-preferred or restricted drug or transition the member to an alternative therapy. Multiple Continuation of Therapy overrides will not be approved for the same drug; OR
- If the member has an existing approved prior authorization (PA) for the non-preferred or restricted drugs, then the member’s previously approved PA will be approved until the PA expires; OR
- If the member has received a prescribed drug to treat a mental illness or emotional disturbance as defined by Minnesota Statute 62Q.527, the member may continue to receive coverage for such prescribed drugs for up to one year.

Continuation of Therapy criteria overrides are not available to bypass generic or biosimilar substitution (if applicable).

Free goods/Pharmaceutical Samples Policy:
The use of free goods or pharmaceutical samples will not be considered as meeting the 90-day treatment requirement for Continuation of Therapy overrides. A member, after meeting all conditions for cash pay, must pay for the entire cost of the non-covered prescription.

REFERENCES
Step Therapy Supplement

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

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL

The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent 
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient's medication history include the required prerequisite/preferred agent(s) 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 required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) 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

Length of Approval: As per program specific criteria