



Effective Date: 11/01/2016
Last P&T Approval/Version: 01/26/2022
Next Review Due By: 01/2023
Policy Number: C9837-A

Pulmonary Arterial Hypertension (PAH)

PRODUCTS AFFECTED

Endothelin-ReceptorAntagonists (ERAs)

Letairis (ambrisentan) Tracleer (bosentan) Opsumit (macitentan), ambrisentan, bosentan

Phosphodiesterase type 5 inhibitors (PDE-5 inhibitors)

Adcirca(tadalafil), ALYQ (tadalafil), Revatio (sildenafil), sildenafil, tadalafil

Soluble Guanylate Cyclase Stimulator

Adempas (riociguat)

Prostanoids/prostacyclin therapies

Uptravi (selexipag), Epoprostenol, Orenitram (treprostinil extended-release tablets), Tyvaso (treprostinil inhalation solution), Veletri (epoprostenol for injection), Remodulin (treprostinil injection), Ventavis (iloprost), Flolan (epoprostenol for injection)

COVERAGE POLICY

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

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

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes.

Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive

DIAGNOSIS:

Pulmonary Hypertension, Chronic Thromboembolic Pulmonary Hypertension, Pulmonaryhypertension associated with interstitial lung disease

REQUIRED MEDICAL INFORMATION:

This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be

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Drug and Biologic Coverage Criteria

determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review

FOR Phosphodiesterase type 5 inhibitors (PDE-5 inhibitors) Adcirca (tadalafil), Revatio (sildenafil), sildenafil ONLY:

FOR NEW YORK HEALTHPLAN MEMBERS ONLY: Reviewer MUST check the Erectile Dysfunction Verification System (EDVS) for each request to determine member's sex offender status. IF a member is on the sex offender list the request must be forwarded to the medical director AND provider must provide the rationale for prescribing a PDE-5 inhibitors and note the reason(s) why alternative treatment options are inappropriate to treat the enrollee's health condition. Before issuing an adverse determination for a prescribed PDE5 inhibitor, the Medical Director must make reasonable attempts to engage in a peer-to-peer discussion with the requesting provider to understand the reasons behind the need for prescribing the requested PDE5 inhibitor or drug. The Medical Director may extend the review time, if requested by the provider or patient, or if such extension is in the best interest of the patient's health condition.

For after-hours, holiday, and weekend pharmacy requests for prescription PDE5 inhibitors Molina Healthcare, Inc can authorize a seventy-two (72) hour emergency supply of the prescription PDE5 inhibitor and must note within the authorization file that the drug is prescribed to treat a condition other than sexual or erectile dysfunction and that the drug has been approved by the FDA to treat that condition. The case must still be sent to the Medical director for checking the EDVS status of the member, as soon as possible on the next business day.

A. PULMONARY ARTERIAL HYPERTENSION:

1. (a) The member has a diagnosis of PAH (WHO Group 1) confirmed by a right heart catheterization and results confirm all the following: Mean pulmonary arterial pressure (mPAP) >20 mm Hg at rest AND Pulmonary capillary wedge pressure (PCWP) AND ≤ 15 mm Hg AND Pulmonary vascular resistance (PVR) ≥ 3 Wood units
OR
(b) The member has a diagnosis of PAH (WHO Group 1) and has a contraindication to right heart catheterization due to: Infection at the insertion site, the presence of a right ventricular assist device, insertion during cardiopulmonary bypass, coagulopathy (international normalized ratio >1.5), thrombocytopenia (platelet count <50,000/microl), electrolyte disturbances (hypo- or hyper-kalemia, -magnesemia, -natremia, -calcemia), and severe acid-base disturbances (eg, pH <7.2 or >7.5) which cannot be corrected or considered high-risk for pulmonary artery catheterization
AND
(c) Member diagnosed by echocardiogram showing mPAP >20 mm Hg or acute vasoreactivity test and other underlying causes of pulmonary hypertension has been ruled out
AND
2. Medication requested for treatment is consistent with its own FDA- labeled approved indicated WHO functional class (see Appendix)
AND
3. FOR ORENITAM (TREPROSTINIL) and UPTRAVI (SELEXIPAG) ONLY:
(a) member has tried or is currently receiving two oral therapies for PAH from two of the three following different categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor, one endothelin receptor antagonist (ERA), OR Adempas (riociguat)
OR
(b) Member is receiving or has received in the past for PAH one prostacyclin therapy, or a prostacyclin receptor agonist for PAH.
AND
4. FOR ADCIRCA, ALYQ, REVATIO OR SILDENAFIL ONLY: The member will not be taking another PDE5 inhibitor at the same time as the requested therapy

Drug and Biologic Coverage Criteria

AND

5. FOR REQUESTS FOR OPSUMIT (MACITENTAN): Documentation of a trial and failure or contraindication to Letairis (ambrisentan) and Tracleer (bosentan)
AND
6. IF REQUEST IS FOR BRAND PRODUCTS WITH GENERICS AVAILABLE: Documentation the patient has failed a trial of the respective generic product and/or the patient cannot take the respective generic product due to a formulation difference in the active ingredient or due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives between the brand and the generic product which would result in a significant allergy or serious adverse reaction per the prescribing physician [DOCUMENTATION REQUIRED]].

B. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)- ADEMPAS ONLY:

1. (a) Documentation member has been diagnosed as inoperable by a center specializing in CTEPH or pulmonary endarterectomy (PEA)
OR
(b) Documentation member been diagnosed as recurrent or persistent CTEPH after PEA
AND
2. Adempas (riociguat) will NOT be administered with phosphodiesterase (PDE)-5 inhibitor ornitrates

C. PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL LUNG DISEASE- TYVASO ONLY

1. Documentation that member has a diagnosis of an interstitial lung disease [examples: Idiopathic pulmonary fibrosis (IPF) or pulmonary fibrosis (PF); Combined pulmonary fibrosis and emphysema (CPFE); Connective tissue disease (CTD)]
AND
2. Documentation that member has Group 3 pulmonary hypertension confirmed by ONE of the following:
(a) Right heart catheterization and results confirm all the following: Mean pulmonary arterial pressure (mPAP) >25 mm Hg at rest AND Pulmonary capillary wedge pressure (PCWP) <15mm Hg AND Pulmonary vascular resistance (PVR) >3 Wood units
OR
(b) The member has a diagnosis of pulmonary hypertension and has a contraindication to right heart catheterization due to: Infection at the insertion site, the presence of a right ventricular assist device, insertion during cardiopulmonary bypass, coagulopathy (international normalized ratio >1.5), thrombocytopenia (platelet count <50,000/microl), electrolyte disturbances (hypo- or hyper-kalemia, -magnesium, -natremia, -calcemia), and severe acid- base disturbances (e.g., pH <7.2 or >7.5) which cannot be corrected or considered high-risk for pulmonary artery catheterization AND Member diagnosed by echocardiogram showing mPAP >25 mm Hg or acute vasoreactivity test and other underlying causes of pulmonary hypertension has been ruled out
AND
3. Documentation of member's baseline 6-minute walk test

CONTINUATION OF THERAPY:

A. PULMONARY ARTERIAL HYPERTENSION:

1. Documentation member is responding to therapy as demonstrated by ONE of the following: Improvement in Six Minute Walking Test or Exercise Capacity, Improvement in WHO Functional Class, decrease in mean pulmonary artery pressure (mPAP), or Increase in Cardiac Index
AND
2. Documentation member is NOT experiencing any adverse effects, drug toxicity or poor response to treatment

Drug and Biologic Coverage Criteria

B. CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH) - ADEMPAS ONLY:

1. Documentation that member's condition has not progressed or worsened on therapy
AND
2. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)

C. PULMONARY HYPERTENSION ASSOCIATED WITH INTERSTITIAL LUNG DISEASE-TYVASO ONLY

1. Documentation that member has had improvement in 6-minute walk test from baseline
AND
2. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance)

DURATION OF APPROVAL:

Initial authorization: 6 months, Continuation of therapy: 12 months

NEW YORK PATIENTS ONLY**PLEASE NOTE: FOR ANY MEMBER ON THE SEX OFFENDER LIST, APPROVAL CAN ONLY BE FOR 30 DAYS PER AUTHORIZATION******

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified cardiologist, pulmonologist, or physician affiliated at a center of expertise in the diagnosis of pulmonary arterial hypertension. FOR ADEMPAS: prescriber has fulfilled the Adempas REMS requirements for certification

AGE RESTRICTIONS:

No requirement

QUANTITY:

Adcirca (tadalafil), Alyq (tadalafil) 20 mg tablet 60 tabs per 30 days

Adempas (riociguat) 0.5 mg, 1mg, 1.5mg, 2mg, or 2.5mg tablet 90 tabs per 30 days

Letairis (ambrisentan) 5 mg or 10mg tablet 30 tabs per 30 days

Opsumit (macitentan) 10 mg tablet 30 tabs per 30 days

Orenitram (treprostinil): determine by tolerability, 90 tabs per 30 days

Revatio (sildenafil): 20 mg tablet 3 tablets per day OR 10 mg/mL oral suspension 2 bottles (224 mL)/30 days

Tracleer (bosentan) 62.5 mg or 125mg tablet 60 tabs per 30 days

Tyvaso (inhaled treprostinil) 0.6 mg/mL System Starter Kit 1 kit/180 days or 0.6 mg/mL System

Refill kit -1 package of 28 ampules/28 days or 4 pack Carton 7 packages of 4 ampules/28 days

Upravi (selexipag) tabs Titration pack 1 pack/180 days 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg or 1600 mcg tablet - 2 tablets per day

Ventavis (iloprost) 10 mcg/mL or 20 mcg/mL - 9 packages of 30 ampules/30 days

NOTE: For Upravi and Orenitram: authorizations may occur in small quantities per strength to allow for titration as prescribed

PLACE OF ADMINISTRATION:

The recommendation is that inhalation medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Drug and Biologic Coverage Criteria

Note: Site of Care Utilization Management Policy applies for epoprostenol (generic for Flolan), Flolan (epoprostenol), Remodulin (treprostinil sodium), Tyvaso (treprostinil). For information on site of care, see [Specialty Medication Administration Site of Care Coverage Criteria \(molinamarketplace.com\)](https://www.molinamarketplace.com/specialty-medication-administration-site-of-care-coverage-criteria)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Oral, Intravenous, Inhalation

DRUG CLASS:

Pulmonary Hypertension

FDA-APPROVED USES:

Adcirca (tadalafil): indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

Adempas (riociguat): indicated for: 1. Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class; 2. Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

Flolan (epoprostenol): indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

Letairis (ambrisentan): indicated for the treatment of adults with pulmonary arterial hypertension World Health Organization [WHO] Group 1.

Remodulin (treprostinil injection): indicated for treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to diminish symptoms associated with exercise and for patients who require transition from epoprostenol, to reduce the rate of clinical deterioration.

Revatio (sildenafil): indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening.

Opsumit (macitentan): indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH

Orenitram (treprostinil extended-release tablets): indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to delay disease progression and to improve exercise capacity.

Tracleer (bosentan): indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) 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%).
- 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

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Tyvaso (treprostinil inhalation solution): indicated for:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

Uptravi (selexipag): indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to delay disease progression and reduce the risk of hospitalization

Ventavis (iloprost): indicated for the treatment of PAH (World Health Organization [WHO] Group 1) to improve exercise tolerance, symptoms (NYHA Class), and lack of deterioration

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:

Treatment algorithm. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; DPAH: drug-induced PAH; CCB: calcium channel blocker; PCA: prostacyclin analogue; PH: pulmonary hypertension. ^a: 2015 ESC/ERS PH guidelines Table 16; ^b: 2015 ESC/ERS PH guidelines Table 17; ^c: 2015 ESC/ERS PH guidelines Table 18; ^d: 2015 ESC/ERS PH guidelines Table 13; ^e: 2015 ESC/ERS PH guidelines Table 19; ^f: 2015 ESC/ERS PH guidelines Table 20; ^g: 2015 ESC/ERS PH guidelines Table 14; ^h: 2015 ESC/ERS PH guidelines Table 21; ⁱ: maximal medical therapy is considered triple combination therapy including a s.c. or an i.v. PCA (i.v. preferred in high-risk status); ^j: 2015 ESC/ERS PH guidelines

Risk stratification and medical therapy of pulmonary arterial hypertension

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European Respiratory Journal 2019 53: 1801889; DOI: 10.1183/13993003.01889-2018

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Adempas, a soluble guanylate cyclase (sGC) stimulator, is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) [World Health Organization {WHO} Group 4] after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class. *Adempas* is also indicated for the treatment of adults with pulmonary arterial hypertension (PAH) [WHO Group 1], to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy in WHO Group 1 PAH was established in patients receiving *Adempas* as monotherapy or in combination with endothelin receptor antagonists (ERAs) or prostanoids. Studies establishing effectiveness included mainly patients with WHO functional class II or III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%). The starting dose of *Adempas* is 1 mg three times daily (TID) and can be titrated to 2.5 mg TID.

Tracleer, *Letairis* and *Opsumit* are oral endothelin receptor antagonists (ERAs) that are used for the treatment of pulmonary arterial hypertension (PAH). *Tracleer*, which is given twice daily (BID), is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) to improve exercise ability and decrease the rate of clinical worsening. Studies establishing the effectiveness included predominantly those with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of

Drug and Biologic Coverage Criteria

idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO Class II symptoms demonstrated reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider if these benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as disease progression occurs.¹ Letairis, which is given once daily (QD), is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening; it is also indicated for use in combination with Adcirca® (tadalafil tablets) to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.² Studies establishing effectiveness included predominantly those with WHO Functional Class II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).² Opsumit, which is given QD, is indicated for the treatment of PAH (WHO Group 1) to delay disease progression.³ Disease progression included: death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsening PAH symptoms, and need for additional PAH treatment). Opsumit also reduced hospitalizations for PAH. All agents are in Pregnancy Category X and have a Boxed Warning regarding teratogenicity. 1-3 Tracleer has a Boxed Warning regarding hepatotoxicity.¹ All agents have a Boxed Warning regarding embryofetal toxicity

Risk Evaluation and Mitigation Strategies (REMS) Program Because of the risk of embryo-fetal toxicity and hepatotoxicity (Tracleer) associated with Tracleer, Letairis, Opsumit therapy, Tracleer, Letairis, Opsumit are available through a restricted program under the REMS. Under the REMS, only certified healthcare providers and pharmacies may prescribe and distribute Tracleer, Letairis, Opsumit

Epoprostenol injection is a prostacyclin vasodilator. It is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to improve exercise capacity. Studies establishing the effectiveness predominately included patients with New York Heart Association (NYHA) Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases. Several studies have noted beneficial effects with epoprostenol therapy. Epoprostenol is given by intravenous infusion through a central venous catheter

Ventavis and Tyvaso are both inhaled prostacyclin vasodilators indicated for the treatment of pulmonary arterial hypertension (PAH). Ventavis, which is given six to nine times per day, is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (based on New York Heart Association [NYHA] Class), and lack of deterioration. Studies establishing effectiveness involved mainly patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%). Tyvaso, which is given four times per day, is indicated for the treatment of PAH (WHO Group 1) to improve exerciseability.² Studies establishing effectiveness mainly included those with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). An updated treatment algorithm (2013) by the 2nd World Symposium on Pulmonary Hypertension (WSPH) states that patients with Functional Class II should be treated initially with oral therapies (e.g., Adempas® [riociguat tablets], sildenafil [Revatio®], generics {Note: brand name Revatio injection also available}, Adcirca® [tadalafil tablets], Opsumit® [macitentan tablets], Tracleer® [bosentan tablets], and Letairis® [ambrisentan tablets]).⁷ Ventavis and Tyvaso are recommended for patients in Functional Class III and IV. In situations of inadequate response, combination therapy (including double or triple therapy) is recommended.

Orenitram, an oral prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to improve exercise capacity. The trial that established the efficacy of Orenitram included mainly patients with WHO functional class II to III symptoms. The prescribing information notes that Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use requires further study. The recommended starting dose is 0.25 mg twice daily (BID) with food, taken approximately 12 hours apart. Dosing is individualized and titrated to response and tolerability; increase in increments of 0.25 to 0.5 mg BID every 3 to 4 days.

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

Remodulin is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to diminish symptoms associated with exercise. Studies establishing the effectiveness involved those with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). *Remodulin* may be administered via continuous subcutaneous (SC) infusion or continuous intravenous infusion. However, due to the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for those intolerant of the SC, or in whom these risks are still considered acceptable. In those with PAH requiring transition from epoprostenol injection, *Remodulin* is indicated to diminish the rate of clinical deterioration. The risks and benefits of each agent should be considered carefully before transition.¹ Several trials have shown benefits of *Remodulin* therapy.

Uptravi (*selexipag*), an oral prostacyclin receptor agonist, is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to delay disease progression and reduce the risk of hospitalization. The trial that established the efficacy of *selexipag* included mainly patients with WHO functional class II to III symptoms. The recommended starting dose is 200 mcg twice daily (BID) and may be more tolerable when taken with food. Dosing is individualized and titrated to tolerability; increased in increments of 200 mcg weekly to up to 1600 mcg twice daily. Those with moderated hepatic impairment should begin with 200 mcg and only dose once daily. *Selexipag* is not recommended to be used with those that have severe hepatic impairment. *Selexipag* is not to be chewed, crushed, or split.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of pulmonary arterial hypertension therapies are considered experimental/investigational and therefore will follow the Molina Healthcare, Inc. off-label policy.

Contraindications to *Adcirca* (tadalafil) include concomitant use of organic nitrates or guanylate cyclase (GC) stimulators. Contraindications to *Adempas* (riociguat) include: pregnancy, use with nitrates or nitric oxide donors in any form, use with PDE inhibitors, patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators, and pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP). Contraindications to *Letairis* (ambrisentan) include pregnancy and idiopathic pulmonary fibrosis. Contraindications to *Tracleer* (bosentan) includes pregnancy, use with cyclosporine, use with glyburide, and hypersensitivity. Contraindications to *Opsumit* (macitentan) include pregnancy.

Drug and Biologic Coverage Criteria

Contraindications to Orenitram (treprostinil) includes severe hepatic impairment (Child Pugh Class C). Contraindications to Flolan (epoprostenol sodium) include heart failure with reduced ejection fraction and hypersensitivity to Flolan and any of its ingredients. Contraindications to Revatio (sildenafil) include use with organic nitrates or riociguat and history of hypersensitivity reaction to sildenafil or any component of the tablet, injection or oral suspension.

OTHER SPECIAL CONSIDERATIONS:

Treatment Guidelines The 6th World Symposium on Pulmonary Hypertension evidence-based treatment algorithm:

Initial approach

- After confirmation of the diagnosis of the treatment-naïve PAH patient in an expert centre, the suggested initial approach is the adoption of *general measures* and the initiation of *supportive therapy* (2015 ESC/ERS PH guidelines).
- *Acute vasoreactivity testing* should be performed to predict response to calcium channel blocker (CCBs) only in patients with IPAH, HPAH, and PAH associated with drugs and toxin use. Vasoreactive patients (see the Task Force article by Simonneau *et al.* in this issue of the *European Respiratory Journal*) should be treated with *high doses (progressively titrated) of CCBs*; adequate response should be confirmed after 3–6 months of treatment (2015 ESC/ERS PH guidelines). *Adequate treatment response to high doses of CCBs* is considered WHO FC I/II with sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only. Vasoreactive patients without an adequate treatment response to high doses of CCBs should be treated with approved PAH medications according to the non-vasoreactive patients' treatment strategy.
- *Non-responders to acute vasoreactivity testing who are at low or intermediate risk* should be treated with *initial oral combination therapy with an ERA and a PDE5i* (2015 ESC/ERS PH guidelines)
- Some specific PAH subsets in which the efficacy/safety ratio of initial combination therapy is not established should be treated with initial monotherapy.

Recommendations for initial monotherapy are reported in the 2015 ESC/ERS PH guidelines

- If initial monotherapy is chosen, as head-to-head comparisons among different compounds are not available, no evidence-based first-line monotherapy can be proposed. The choice of drug may depend on a variety of factors, including approval status, labeling, route of administration, side-effect profile, potential interaction with background therapies, patient preferences, comorbidities, physician experience and cost.
- *In non-vasoreactive and treatment-naïve patients at high risk*, initial combination therapy including *i.e.*, PCAs is recommended (2015 ESC/ERS PH guidelines). Intravenous epoprostenol receives the strongest recommendation as it has reduced the 3-month rate of mortality in high-risk PAH patients also as monotherapy (2015 ESC/ERS PH guidelines). Alternative types of initial combination therapy may be considered (2015 ESC/ERS PH guidelines). Referral for lung transplantation should also be considered.

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CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Drug and Biologic Coverage Criteria

HCPCS CODE	DESCRIPTION
J1325 J3285 J7686	Injection, epoprostenol, 0.5 mg Injection, treprostinil, 1 mg Treprostinil, inhalation solution, fda-approved final product, non-compounded, administered through dme, unit dose form, 1.74 mg
Q4074	Iloprost, inhalation solution, fda-approved final product, non-compounded, administered through dme, unit dose form, up to 20 micrograms

AVAILABLE DOSAGE FORMS:

Adcirca TABS 20MG	Revatio TABS 20MG
Adempas TABS 0.5MG*	Sildenafil Citrate SOLN 10MG/12.5ML
Adempas TABS 1.5MG*	Sildenafil Citrate SUSR 10MG/ML
Adempas TABS 1MG*	Sildenafil Citrate TABS 20MG
Adempas TABS 2.5MG*	Tadalafil (PAH) TABS 20MG
Adempas TABS 2MG*	Tracleer TABS 125MG*
Alyq TABS 20MG	Tracleer TABS 62.5MG*
Ambrisentan TABS 10MG	Tracleer TBSO 32MG
Ambrisentan TABS 5MG	Treprostinil SOLN 100MG/20ML
Bosentan TABS 125MG	Treprostinil SOLN 200MG/20ML
Bosentan TABS 62.5MG	Treprostinil SOLN 20MG/20ML
Epoprostenol Sodium SOLR 0.5MG	Treprostinil SOLN 50MG/20ML
Epoprostenol Sodium SOLR 1.5MG	Tyvaso SOLN 0.6MG/ML*
Flolan SOLR 0.5MG	Tyvaso Refill SOLN 0.6MG/ML*
Flolan SOLR 1.5MG	Tyvaso Starter SOLN 0.6MG/ML*
Letairis TABS 10MG*	Uptravi SOLR 1800MCG*
Letairis TABS 5MG*	Uptravi TABS 1000MCG*
Opsumit TABS 10MG*	Uptravi TABS 1200MCG*
Orenitram TBCR 0.125MG	Uptravi TABS 1400MCG*
Orenitram TBCR 0.25MG	Uptravi TABS 1600MCG*
Orenitram TBCR 1MG	Uptravi TABS 200MCG*
Orenitram TBCR 2.5MG	Uptravi TABS 400MCG*
Orenitram TBCR 5MG	Uptravi TABS 600MCG*
Remodulin SOLN 100MG/20ML*	Uptravi TABS 800MCG*
Remodulin SOLN 200MG/20ML*	Uptravi TBPK 200 & 800MCG*
Remodulin SOLN 20MG/20ML*	Veletri SOLR 0.5MG
Remodulin SOLN 50MG/20ML*	Veletri SOLR 1.5MG
Revatio SOLN 10MG/12.5ML	Ventavis SOLN 10MCG/ML*
Revatio SUSR 10MG/ML	Ventavis SOLN 20MCG/ML*

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