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Policy Number: C9837-A

Pulmonary Arterial Hypertension (PAH)

PRODUCTS AFFECTED

Endothelin-Receptor Antagonists (ERAs)

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

Phosphodiesterase type 5 inhibitors (PDE-5 inhibitors)

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

Soluble Guanylate Cyclase Stimulator

Adempas (riociguat)

Prostanoids/prostacyclin therapies

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

Activin Signaling Inhibitor

Winrevair (sotatercept)

ERA/PDE-5 Inhibitor Combination

Opsynvi (macitentan and tadalafil)

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.

Drug and Biologic Coverage Criteria

DIAGNOSIS:

Pulmonary Arterial Hypertension, Chronic Thromboembolic Pulmonary Hypertension, Pulmonary hypertension 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 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. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PULMONARY ARTERIAL HYPERTENSION:

1. Documented diagnosis of pulmonary arterial hypertension (PAH)
AND
2. Documentation of member's WHO group and WHO functional class
AND
3. Medication requested for treatment is consistent with its own FDA- labeled WHO functional class (see Appendix)
AND
4. FOR ORENITRAM (TREPASTINIL), UPTRAVI (SELEXIPAG), AND WINREVAIR (SOTATERCEPT) ONLY:
(a) Member has tried or is currently receiving oral therapy (either alone or in combination) for PAH from at least two of the three following different categories, 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
5. FOR ADCIRCA, ALYQ, LIQREV, OPSYNVI, TADLIQ, REVATIO, TADALAFIL OR SILDENAFIL ONLY: The member will not be taking another PDE5 inhibitor at the same time as the requested therapy
AND
6. FOR REQUESTS FOR OPSUMIT (MACITENTAN): Documentation of a trial and failure or contraindication to ambrisentan and bosentan
AND
7. FOR REQUESTS FOR OPSYNVI (MACITENTAN/TADALAFIL): Documentation of inadequate response to all matching therapeutic class formulary/PDL single agents within the requested combination product
AND
8. IF REQUEST IS FOR BRAND PRODUCT WITH GENERIC 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. Documented diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH)

Drug and Biologic Coverage Criteria

AND

2. (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

3. Prescriber attests Adempas (riociguat) will NOT be administered with phosphodiesterase (PDE)-5 inhibitors or nitrates

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

1. Documentation 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

AND

3. Documentation of member's baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal (e.g., 6-minute walk test, NT-proBNP, clinical status) [DOCUMENTATION REQUIRED]

CONTINUATION OF THERAPY:

A. PULMONARY ARTERIAL HYPERTENSION:

1. Documentation that the member has demonstrated a beneficial response to therapy per the prescribing physician (e.g., Improvement in Six Minute Walking Test or Exercise Capacity, Improvement in WHO Functional Class, decrease in mean pulmonary artery pressure [mPAP], Increase in Cardiac Index, etc.)

AND

2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

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

1. Documentation that member's condition has not progressed or worsened on therapy

AND

2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

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

1. Documentation that the member has demonstrated a beneficial response to therapy per the prescribing physician (e.g., improvement in 6-minute walk test, improvement in NT-proBNP, lack of disease progression [hospitalization, worsening 6MWT, lung transplant]) [DOCUMENTATION REQUIRED]

AND

2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

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

MOLINA REVIEWER NOTE: For NY Medicaid, please see Appendix.

PRESCRIBER REQUIREMENTS:

Prescribed by a board-certified cardiologist, pulmonologist, or physician affiliated with a center of expertise in pulmonary arterial hypertension.

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Drug and Biologic Coverage Criteria

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

Liqrev (sildenafil): 2 bottles (244mL)/30 days

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

Opsynvi (macitentan/tadalafil): 10/20mg or 10/40mg once daily

Orenitram (treprostinil): determined 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

Tadliq (tadalafil): 2 bottles (300mL)/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

Uptravi (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

Winrevair (sotatercept) starting dose 0.3 mg/kg, target dose 0.7 mg/kg subcutaneous injection every 3 weeks

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

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

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 injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location.

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.

Note: Site of Care Utilization Management Policy applies for 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)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Oral, Intravenous, Inhalation, Subcutaneous

DRUG CLASS:

Pulmonary Hypertension – Prostacyclin Receptor Agonist, Pulm Hyperten-Soluble Guanylate Cyclase Stimulator (sGC), Pulmonary Hypertension – Phosphodiesterase Inhibitors, Pulmonary Hypertension – Endothelin Receptor Antagonists, Prostaglandin Vasodilators, Pulmonary Hypertension – Activin

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Drug and Biologic Coverage Criteria Signaling Inhibitor

FDA-APPROVED USES:

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

Adempas (riociguat): indicated for the 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
- Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.

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

Letairis (ambrisentan): indicated for the treatment of pulmonary arterial hypertension (PAH) (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. Indicated in pediatric patients 1 to 17 years old for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underlie improvements in exercise.

Liqrev (sildenafil): indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [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.

Opsynvi (macitentan and tadalafil): indicated for chronic treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adult patients of WHO functional class (FC) II-III. Individually, macitentan reduces the risk of clinical worsening events and hospitalization, and tadalafil improves exercise ability.

Tracleer (bosentan): indicated for the treatment of pulmonary arterial hypertension (PAH) (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.

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%).

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Drug and Biologic Coverage Criteria

- 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 for PAH.

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

Winrevair (sotatercept): indicated for the treatment of adults with pulmonary arterial hypertension (PAH, WHO Group 1) to increase exercise capacity, improve WHO functional class (FC) and reduce the risk of clinical worsening events.

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:

Reserved for State specific information. Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.

State Specific Information

State Medicaid

New York

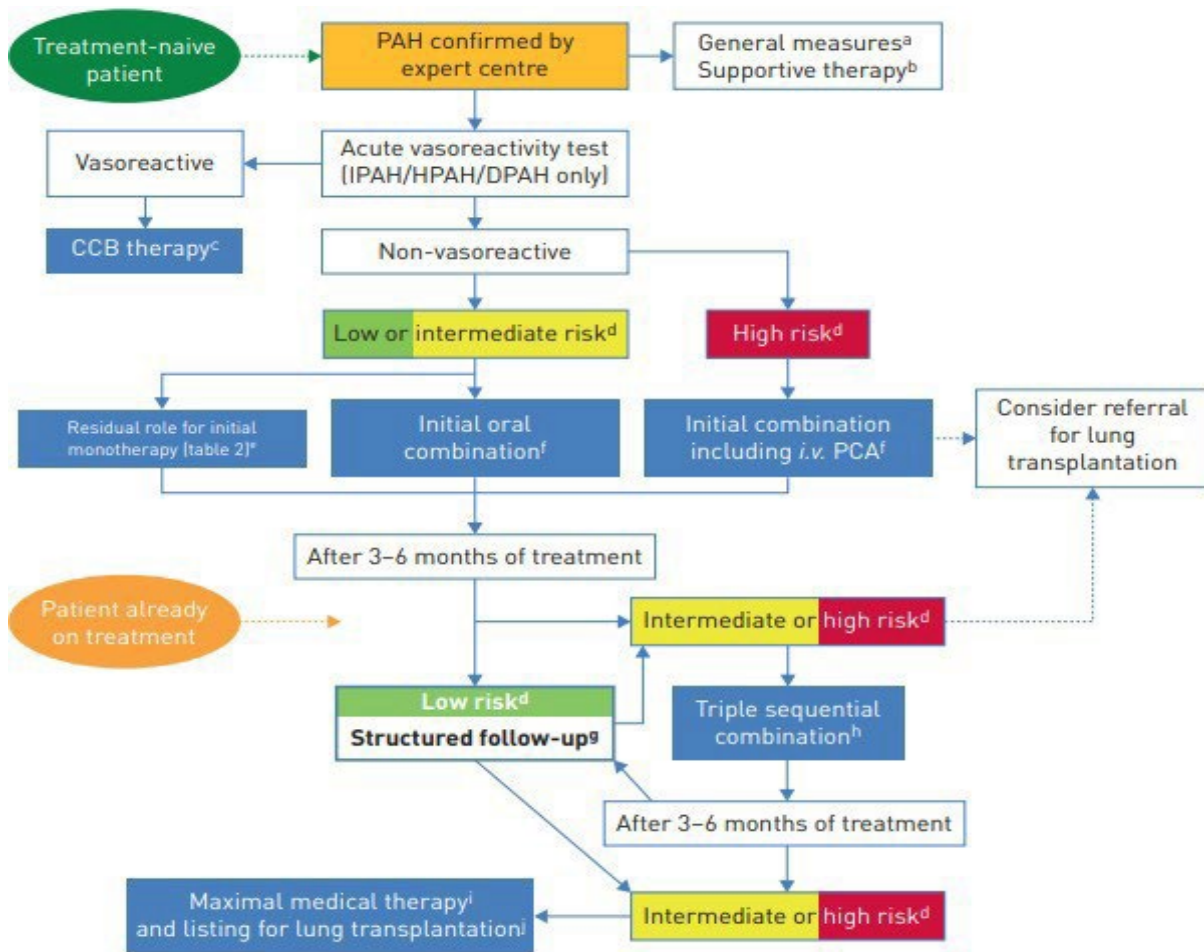
FOR Phosphodiesterase type 5 inhibitors (PDE-5 inhibitors) Adcirca (tadalafil), ALYQ (tadalafil), Opsynvi (macitentan/tadalafil), Tadliq (tadalafil), Revatio (sildenafil), sildenafil, tadalafil ONLY:

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.

FOR ANY MEMBER ON THE SEX OFFENDER LIST, APPROVAL CAN ONLY BE FOR 30 DAYS PER AUTHORIZATION.

Drug and Biologic Coverage Criteria



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 Table 22

Risk stratification and medical therapy of pulmonary arterial hypertension
 Nazzareno Galiè, Richard N. Channick, Robert P. Frantz, Ekkehard Grünig, Zhi Cheng Jing, Olga Moiseeva, Ioana R. Preston, Tomas Pulido, Zeenat Safdar, Yuichi Tamura, Vallerie V. McLaughlin *European Respiratory Journal* 2019 53: 1801889; DOI: 10.1183/13993003.01889-2018

Brand (generic)	WHO Group	WHO Functional Class
Adcirca (tadalafil)	Group 1 PAH	Functional Class II-III
Adempas (riociguat)	Group 1 PAH	Functional Class II-III
	Group 4 CTEPH	n/a
Alyq (tadalafil)	Group 1 PAH	Functional Class II-III
Flolan (epoprostenol)	Group 1 PAH	Functional Class III-IV

Drug and Biologic Coverage Criteria

sodium)		
Letairis (ambrisentan)	Group 1 PAH	Functional Class II-III
Opsumit (macitentan)	Group 1 PAH	Functional Class II-III
Orenitram (treprostinil)	Group 1 PAH	Functional Class II-III
Opsynvi (macitentan and tadalafil)	Group 1 PAH	Functional Class II-III
Remodulin (treprostinil)	Group 1 PAH	Functional Class II-IV
Revatio (sildenafil)	Group 1 PAH	Functional Class II-III
Tracleer (bosentan)	Group 1 PAH	Functional Class II-IV
Tyvaso (treprostinil)	Group 1 PAH	Functional Class III
	Group 3 PH-ILD	n/a
Upravi (selexipag)	Group 1 PAH	Functional Class II-III
Veletri (epoprostenol)	Group 1 PAH	Functional Class II-IV
Ventavis (iloprost)	Group 1 PAH	Functional Class III-IV
Winrevair (sotatercept)	Group 1 PAH	Functional Class II-III

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.

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

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 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

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Drug and Biologic Coverage Criteria

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.

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®

Drug and Biologic Coverage Criteria

[generic], Veletri®). 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.

Winrevair (sotatercept) is the first activin signaling pathway inhibitor approved for PAH. The approval of Winrevair was based on the randomized, double-blind, Phase 3 STELLAR trial, which evaluated the efficacy and safety of Winrevair compared with placebo as an add-on to standard-of-care background. Patients who received Winrevair demonstrated improvement in 6-minute walk distance at 24 weeks compared with those who received placebo. The trial also met 8 out of 9 secondary measures, including a reduction in time to clinical worsening or death in the treatment group versus placebo. Ongoing trials of Winrevair in PAH include HYPERION, ZENITH, and SOTERIA, which are early-intervention, later-intervention, and long-term outcomes studies, respectively.

Opsynvi (macitentan and tadalafil) is the first combination product for PAH and is a combination of drugs actively in the market for PAH treatment. Opsynvi was approved through the 505(b)(2) pathway based on safety and efficacy data for Opsumit and Adcirca. Additionally, a randomized, double-blind, active-control phase 3 trial was conducted that compared Opsynvi to macitentan and tadalafil monotherapy. Opsynvi showed greater efficacy than either monotherapy.

Drug and Biologic Coverage Criteria

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

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, ALYQ, Tadiq, tadalafil include: concomitant use of organic nitrates or guanylate cyclase (GC) stimulators, history of known serious hypersensitivity reaction to tadalafil or Cialis.

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) include: pregnancy, use with cyclosporine, use with glyburide, and hypersensitivity.

Contraindications to Opsumit (macitentan) include: pregnancy, and hypersensitivity.

Contraindications to Opsyvni (macitentan and tadalafil) include: Pregnancy, hypersensitivity, concomitant organic nitrates, concomitant guanylate cyclase (GC) stimulators.

Contraindications to Orenitram (treprostinil) include: severe hepatic impairment (Child Pugh Class C).

Contraindications to Tyvaso (treprostinil), Tyvaso DPI (treprostinil), and Remodulin (treprostinil) include: No labeled contraindications.

Contraindications to Flolan (epoprostenol sodium) include: heart failure with reduced ejection fraction and hypersensitivity to Flolan and any of its ingredients.

Contraindications to Veletri (epoprostenol) include: congestive heart failure due to severe left ventricular systolic dysfunction, pulmonary edema, hypersensitivity to the drug or to structurally related compounds.

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.

Contraindications to Upravi (selexipag) include: concomitant use with strong CYP2C8 inhibitors, hypersensitivity to the active substance or to any of the excipients.

Contraindications to Ventavis (iloprost) include: No labeled contraindications.

Contraindications to Winrevair (sotatercept) include: No labeled contraindications.

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-naive 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

Drug and Biologic Coverage Criteria

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.

Nazzareno Galiè, Richard N. Channick, Robert P. Frantz, Ekkehard Grünig, Zhi Cheng Jing, Olga Moiseeva, Ioana R. Preston, Tomas Pulido, Zeenat Safdar, Yuichi Tamura, Vallerie V. Risk stratification and medical therapy of pulmonary arterial hypertension. McLaughlin European Respiratory Journal 2019 53: 1801889; DOI: 10.1183/13993003.01889-2018

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

HCPCS CODE	DESCRIPTION
J1325	Injection, epoprostenol, 0.5 mg
J3285	Injection, treprostinil, 1 mg
J7686	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
Adempas TABS 0.5MG, 1MG, 1.5MG, 2MG, 2.5MG
Alyq TABS 20MG
Ambrisentan TABS 5MG, 10MG
Bosentan TABS 62.5MG, 125MG
Epoprostenol Sodium SOLR 0.5MG, 1.5MG
Flolan SOLR 0.5MG, 1.5MG
Letairis TABS 5MG, 10MG
Liqrev SUSP 10MG/ML
Opsumit TABS 10MG
Orenitram Month 1 TEPK 0.125 & 0.25MG
Orenitram Month 2 TEPK 0.125 & 0.25MG
Orenitram Month 3 TEPK 0.125 & 0.25 & 1MG
Orenitram TBCR 0.125MG, 0.25MG, 1MG, 2.5MG, 5MG
Remodulin SOLN 20MG/20ML, 50MG/20ML, 100MG/20ML, 200MG/20ML
Revatio SOLN 10MG/12.5ML
Revatio SUSR 10MG/ML

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Drug and Biologic Coverage Criteria

Revatio TABS 20MG
Sildenafil Citrate SOLN 10MG/12.5ML
Sildenafil Citrate SUSR 10MG/ML
Sildenafil Citrate TABS 20MG
Tadalafil (PAH) TABS 20MG
Tadliq SUSP 20MG/5ML
Tracleer TABS 62.5MG, 125MG
Tracleer TBSO 32MG
Treprostinil SOLN 20MG/20ML, 50MG/20ML, 100MG/20ML, 200MG/20ML
Tyvaso DPI Maintenance Kit POWD 16MCG, 32MCG, 48MCG, 64MCG
Tyvaso DPI Maintenance Kt POWD 112X32MCG&112 x48MC
Tyvaso DPI Titration Kit POWD 16 & 32 & 48MCG
Tyvaso DPI Titration Kt POWD 112X16MCG&84X32MCG
Tyvaso Refill SOLN 0.6MG/ML
Tyvaso SOLN 0.6MG/ML
Tyvaso Starter SOLN 0.6MG/ML
Uptravi SOLR 1800MCG
Uptravi TABS 200MCG, 400MCG, 600MCG, 800MCG, 1000MCG, 1200MCG, 1400MCG, 1600MCG
Uptravi Titration TBPK 200 & 800MCG
Veletri SOLR 0.5MG, 1.5MG
Ventavis SOLN 10MCG/ML, 20MCG/ML
Opsynvi TABS 10-20MG, 10-40MG
Winrevair KIT 45MG, 60MG, 2 x 45MG, 2 x 60MG

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Products Affected Required Medical Information Quantity Place of Administration Route of Administration Drug Class FDA-Approved Uses Appendix Background Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q3 2024
REVISION- Notable revisions: Products Affected Continuation of Therapy Duration of Approval Quantity FDA-Approved Uses Appendix Available Dosage Forms References	Q1 2024
REVISION- Notable revisions: Products Affected Required Medical Information Continuation of Therapy Prescriber Requirements Place of Administration Drug Class FDA-Approved Uses Appendix Background Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file