Pulmonary Arterial Hypertension

Revatio® (sildenafil), Remodulin® (treprostinil), Flolan®/ Veletri® (epoprostenol)

(Intravenous/Subcutaneous)

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I. Length of Authorization

Coverage will be provided for six months and is eligible for renewal.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

Drug	Drug strength/formulation	# of Units	Per # of Days	Units/Day
Revatio	10 mg/12.5 mL injection	90 vial	30	3
Flolan/Veletri	0.5 mg injection 1.5 mg injection	56 vials	28	2
Epoprostenol (generic Flolan)	0.5 mg injection 1.5 mg injection	56 vials	28	2
Remodulin	1 mg/mL- 20 mg injection 2.5 mg/mL- 50 mg injection 5 mg/mL- 100 mg injection 10 mg/mL- 200 mg injection	1 vial	30	0.67 mL
Treprostinil	1 mg/mL- 20 mg injection 2.5 mg/mL- 50 mg injection 5 mg/mL- 100 mg injection 10 mg/mL- 200 mg injection	1 vial	30	0.67 mL

B. Max Units (per dose and over time) [HCPCS Unit]:

Flolan/Veletri

- 6 billable units per day

Remodulin

- 7 billable units per day

Revatio

- 3 billable units per day

III. Initial Approval Criteria[1,2,3,4,5,6,7,14,21,22,23,24,25]

Coverage is provided in the following conditions:

- Patient does not have any of the following:
    - Patient is NOT concurrently on organic nitrates (i.e., isosorbide mononitrate, isosorbide dinitrate, nitroglycerin) or riociguat (**Revatio ONLY**)
    - Patient does not have heart failure with reduced ejection fraction (**Flolan ONLY**)
    - Patient does not have congestive heart failure due to severe left ventricular systolic dysfunction OR pulmonary edema (**Veletri ONLY**)

Pulmonary arterial hypertension (PAH) †

- Patient is at least 18 years old (unless otherwise specified):
    - Patient is at least 17 years of age for Remodulin
- Diagnosis confirmed by documented right heart catheterization with ALL of the following:
    - Mean pulmonary artery pressure (mPAP) > 20mm Hg; **AND**
    - Pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg; **AND**
    - Pulmonary vascular resistance (PVR) ≥ 3 wood units (240 dynes-sec/cm^5); **AND**
- Baseline assessment of 6 minute walk test and/or B-type natriuretic peptide plasma levels (NT-proBNP); **AND**
- Diagnosed with pulmonary arterial hypertension and classified as WHO (World Health Organization) Group 1 (See below for description of WHO classification for pulmonary hypertension); **AND**
- Designated as New York Heart Association (NYHA) or World Health Organization (WHO) functional class II-IV (See below for description of functional classes); **AND**
- Patient is treatment-naïve to PAH-specific pharmacotherapy **§**; **AND**
    - Patient is Functional Class II or Functional Class III without evidence of rapid disease progression or poor prognosis; **AND**
        - Patient had an inadequate response to calcium channel blocker therapy or is not a candidate for treatment with a calcium channel blocker (i.e., negative results for acute vasoreactivity, right ventricular failure, or contraindication to calcium channel blocker); **AND**
            - Patient is unwilling or unable to tolerate combination therapy; **AND**
            - Patient will be treated with Revatio monotherapy; **OR**
    - Patient is Functional Class III with evidence of rapid progression of their disease, or other markers of a poor clinical prognosis; **AND**
        - Patient will be treated with continuous IV Flolan, or Veltri; **OR**
        - Patient will be treated with IV or SC Remodulin; **OR**
    - Patient is Functional Class IV; **AND**
        - Patient will be treated with continuous IV Flolan, or Veltri; **OR**
        - Patient will be treated with IV or SC Remodulin; **OR**

- Patient is Functional Class III or IV and had an inadequate clinical response‡ (see criteria below) to monotherapy and will be adding a second class of PAH therapy as one of the following (see PAH pharmacotherapy table below §):
    - Adding Revatio to an intravenous epoprostenol; **OR**
    - Initiating an up-titration of the patient's current dose of IV Flolan or Veltri; **OR**
- Patient is Functional Class III or IV with an inadequate clinical response‡ (see criteria below) to two classes of PAH pharmacotherapy and will be adding a third class of PAH therapy (see PAH pharmacotherapy table below §); **OR**
- Patient is transitioning from Remodulin to Orenitram and using Remodulin (treprostinil) and Orenitram (treprostinil) concurrently

Pulmonary Hypertension Pharmacotherapy §		
Class	**Drug**	**Route of Administration**
Phosphodiesterase-5 inhibitors (PDE5i)	Revatio (Sildenafil) Adcirca (Tadalafil)	IV, Oral Oral
Prostacyclin analogs	Flolan, Veletri (Epoprostenol) Orenitram, Remodulin, Tyvaso (Treprostinil) Ventavis (Iloprost)	IV Oral, IV/SC, Inhaled Inhaled
Endothelial-receptor antagonists (ERA)	Tracleer (Bosentan) Letairis (Ambrisentan) Opsumit (Macitentan)	Oral Oral Oral
Soluble guanylate cyclase stimulators	Adempas (riociguat) ▪ Must NOT be used in combination with PDE5i (e.g., Revatio, Adcirca) or intravenous prostacyclin analogs (e.g., Flolan, Veletri, Remodulin) ▪ *Subcutaneous administration of Remodulin is allowable with Adempas*	Oral
Prostacyclin receptor agonists	Uptravi (selexipag) ▪ May be used in combination with BOTH a PDE5i AND an ERA	Oral

Inadequate Clinical Response Criteria ‡

- Inadequate clinical response for patients who were initially in WHO Functional Class II or III:
  - Resulting clinical status defined as stable and not satisfactory; **OR**
  - Resulting clinical status defined as unstable and deteriorating
- Inadequate clinical response for patients who were initially in WHO Functional Class IV:
  - No rapid improvement to WHO Functional Class III or better; **OR**
  - Resulting clinical status defined as stable and not satisfactory

Reference charts

<u>WHO classification of pulmonary hypertension (PH):</u>

- Group 1 PAH: Pulmonary arterial hypertension (PAH)
- Group 2 PH: Pulmonary hypertension owing to left heart disease
- Group 3 PH: Pulmonary hypertension owing to lung diseases and/or hypoxia
- Group 4 PH: Chronic thromboembolic pulmonary hypertension (CTEPH)
- Group 5 PH: Pulmonary hypertension with unclear multifactorial mechanisms

New York Heart Association (NYHA) Functional Classification

- Class I: No symptoms with ordinary physical activity.
- Class II: Symptoms with ordinary activity. Slight limitation of activity.
- Class III: Symptoms with less than ordinary activity. Marked limitation of activity.
- Class IV: Symptoms with any activity or even at rest.

World Health Organization (WHO) Functional Assessment Classification

- Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
- Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

† FDA-labeled indication(s)

Note: Clinical review for use in pediatric patients, unless specified above, will occur on a case by case basis

IV. Renewal Criteria[1,2,3,4,5,6,7,14,21,22,23,24,25]

Coverage can be renewed based on the following criteria:

- Patient continues to meet criteria identified in section III; **AND**
- Disease response as determined by one or more of the following:
  - Progress towards an improvement in WHO functional class status
  - Improvement in right ventricular function (based on echocardiogram or cardiac MRI)
  - Improvement (from baseline) on the 6 minute walk distance
  - Improvement in B-type natriuretic peptide plasma levels; **AND**

Revatio®

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: pulmonary edema, worsening of pulmonary veno-occlusive disease (PVOD), hearing loss, visual loss, hypotension; epistaxis; priapism,etc.

Flolan®, Veletri®

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: anticoagulation abnormalities/risk of bleeding, pulmonary edema, vasodilation reactions (hypotension, flushing, nausea, vomiting, dizziness, or headache), etc.

Remodulin®

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: catheter-blood stream infections (BSIs), sepsis, severe infusion site reactions, symptomatic hypotension; anticoagulation abnormalities/risk of bleeding, etc.

V. Dosage/Administration[1,2,3,4,21]

Indication	Dose
Revatio® (intravenous injection)	2.5 mg or 10 mg (12.5 mL) three times a day administered as an intravenous bolus injection
Flolan®/ Veletri® (continuous intravenous infusion)	Initiate at 2 ng/kg/min. Increase infusion by 1- to 2-ng/kg/min increments every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established. Epoprostenol must be infused via a central venous catheter.
Remodulin® (continuous subcutaneous or intravenous infusion)	1.25 ng/kg/min (or 0.625 ng/kg/min if not tolerated or in patients with mild or moderate hepatic insufficiency); dose increase based on clinical response (increments of 1.25 ng/kg/min per week for the first 4 weeks of treatment, then 2.5 ng/kg/min per week for the remaining duration of the infusion. Transitioning from epoprostenol: • Initiate Remodulin at a recommended dose of 10% of the current epoprostenol dose • Decrease the dose of epoprostenol while simultaneously increasing the dose of Remodulin, based on response

VI. Billing Code/Availability Information

Drug	J-Code	Billable Units (BU)	Drug strength/formulation	NDC
Revatio* (Pfizer)	J3490	10 mg = 1 BU	10 mg/12.5mL injection	00069-0338-xx
Flolan* (GSK)	J1325§	0.5 mg= 1 BU	0.5 mg injection	00173-0517-xx
			1.5 mg injection	00173-0519-xx
Veletri* (Actelion Pharm)	J1325§	0.5 mg = 1 BU	0.5 mg injection	66215-0403-xx
			1.5 mg injection	66215-0402-xx
Remodulin* (United Therapeutics)	J3285§	1 mg = 1 BU	1 mg/mL – 20 mg injection	66302-0101-xx
			2.5 mg/mL - 50 mg injection	66302-0102-xx
			5 mg/mL - 100 mg injection	66302-0105-xx
			10 mg/mL - 200 mg injection	66302-0110-xx

* *Generic available*

§ Sterile diluent for epoprostenol, 50mL, should be billed under HCPCS code S0155 or J3490

VII. References

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Appendix 1 – Covered Diagnosis Codes

ICD-10	Description
I27.0	Primary pulmonary hypertension
I27.1	Kyphoscoliotic heart disease
I27.20	Pulmonary hypertension, unspecified
I27.21	Secondary pulmonary arterial hypertension
I27.83	Eisenmenger's syndrome
I27.89	Other specified pulmonary heart diseases
I27.9	Pulmonary heart disease, unspecified
M34.0	Progressive systemic sclerosis
M34.1	CR(E)ST syndrome
M34.9	Systemic sclerosis, unspecified

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs) and Articles may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/Article): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC