

Department:	Pharmacy Management	Original Approval:	12/24/2015
Policy #:	PM122	Last Approval:	06/14/2018
Title:	Treprostinil (Remodulin®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Treprostinil (Remodulin): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Prescribed by or in consultation with a cardiologist or pulmonologist - Labs/diagnostics -Medication list (current and past) to include start and end dates of all Pulmonary Arterial Hypertension therapies -Dosing and duration -Weight.

BACKGROUND

Remodulin is a prostacyclin vasodilator. It is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1, to diminish symptoms associated with exercise. Studies establishing effectiveness involved patients 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%). It is also indicated for patients who require transition from Flolan® (epoprostenol injection) to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.¹ Several trials have shown benefits of Remodulin therapy.¹⁻⁸

Remodulin is supplied in 20 mL multidose vials containing 20 mg, 50 mg, 100 mg, or 200 mg of treprostinil. Remodulin can be given as supplied or diluted for intravenous infusion with Sterile Water for Injection, 0.9% Sodium Chloride injection, and Sterile Diluent for Remodulin, Flolan or epoprostenol sodium. Remodulin is given subcutaneously (SC) as a continuous infusion or intravenously as a continuous infusion.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	<i>Continue to criteria for approval below.</i>
Medicare Members	<i>Step-utilization of Part D drugs not required.</i>

Coverage of Remodulin is recommended in those who meet the following criteria:

FDA-Approved Indications

Criteria for PAH is divided into patients initiating therapy (1A) and those who have already been started on Remodulin therapy (1B).

1A. Pulmonary Arterial Hypertension (PAH) (WHO Group 1) for Patients not Currently Receiving Remodulin.

Criteria. *The patient must meet the following criteria (A, B, C, D, AND E):*

- A)** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- B)** The patient has had a right heart catheterization to confirm the diagnosis of PAH and the results of the right heart catheterization are as follows: mean pulmonary arterial pressure (mPAP) > 25 mm Hg at rest; pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg; and pulmonary vascular resistance (PVR) > 3 Wood units; AND
- C)** The patient meets one of the following criteria (i or ii):
 - i.** The patient is in Functional Class III or IV; OR
 - ii.** The patient is in Functional Class II and meets ONE of the following criteria [1 or 2]:
 - 1.** The patient has tried or is currently receiving one oral agent for PAH (e.g., Tracleer® [bosentan tablets], Letairis® [ambrisentan tablets], Opsumit® [macitentan tablets], Adempas® [riociguat tablets], Revatio®/Viagra® [sildenafil tablets or injection], Adcirca®/Cialis® [tadalafil tablets], Orenitram™ [treprostinil extended-release tablets]) or Uptravi® [selexipag tablets]); OR
The patient is unable to take any of the agents above (e.g., those with liver abnormalities [Tracleer], patients of childbearing potential [Tracleer, Letairis], concomitantly using nitrates [sildenafil, Adcirca/Cialis], hypotension, drug-drug interactions); OR
 - 2.** The patient has tried one inhaled or parenteral prostacyclin product for PAH (e.g., Ventavis® [iloprost inhalation solution], Tyvaso® [treprostinil inhalation solution], epoprostenol injection); AND
- D)** The patient has WHO Group 1 PAH; AND
- E)** Patients with idiopathic PAH must meet one of the following criteria (i, ii, iii, iv or v).
 - i.** The patient had an acute response to vasodilator testing that occurred during the right heart catheterization (defined as a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output) AND has tried one oral calcium channel blocker (CCB) therapy (e.g., amlodipine, nifedipine extended-release tablets); OR
 - ii.** The patient did not have an acute response to vasodilator testing; OR
 - iii.** The patient cannot undergo a vasodilator test; OR
 - iv.** The patient cannot take CCB therapy (e.g., right heart failure, decreased cardiac output); OR
 - v.** The patient has tried one CCB (e.g., amlodipine, nifedipine extended-release tablets).

1B. Pulmonary Arterial Hypertension (WHO Group 1) for Patients Currently Receiving Remodulin.

Criteria. *The patient must meet the following criteria (A OR B):*

- A)** The patient meets all of the following conditions (i, ii, and iii):
- i. The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
 - ii. The patient has had a right heart catheterization to confirm the diagnosis of PAH and the results of the right heart catheterization are as follows: mPAP > 25 mm Hg at rest; PCWP ≤ 15 mm Hg; and PVR > 3 Wood units; AND
 - iii. The patient has WHO Group 1 PAH; OR
- B)** Approve a short-term supply of Remodulin for up to 14 days if the patient does not meet the criteria in 1Ba above or if there is insufficient information available. These cases must be forwarded immediately to the medical director for review. Note: a 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of Remodulin may have severe adverse consequences.

Remodulin is indicated for the treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise.¹ Studies establishing effectiveness included patients with 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%).¹ The World Symposium on Pulmonary Hypertension (WSPH) updated treatment algorithm of PAH recommend subcutaneous Remodulin and intravenous Remodulin in patients WHO Functional Class III or Class IV.¹⁶ Patients in Functional Class II should be treated with an oral agent for PAH (e.g., Tracleer, Opsumit, Letairis, Adempas, sildenafil, Adcirca). American College of Chest Physicians (ACCP) guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend a right heart catheterization to confirm the presence of pulmonary hypertension, establish the diagnosis, and determine PAH disease severity.¹⁰ An American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, the American Thoracic Society (ATS) and the Pulmonary Hypertension Association, note all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to the initiation of therapy.⁹ The current hemodynamic definition of PAH is a mPAP greater than 25 mmHg; a PCWP, left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a PVR greater than 3 Wood units. Acute vasodilator testing should be done in all patients with idiopathic PAH who might be considered potential candidates for long-term calcium channel blocker therapy. Those with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing. The definition of an acute responder is a reduction in mPAP to at least 10 mm Hg or an absolute mPAP of less than 40 mmHg without a decrease in cardiac output.⁹ Abrupt withdrawal of Remodulin may lead to worsening of PAH symptoms and should be avoided.¹ In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Pulmonary Arterial Hypertension (PAH). *Dosing must meet ONE of the following (A OR B):*

- A) In adults, Remodulin is given SC as a continuous infusion or intravenous as a continuous infusion. The preferred route is SC but it can be given by a central intravenous line if the SC route is not tolerated. Therapy is initiated at 1.25 ng per kg per min and is adjusted according to response (PAH symptom relief) or adverse effects. Patients are carefully monitored as the dose is adjusted. In mild or moderate hepatic insufficiency, the initial dose is 0.625 ng per kg per min ideal body weight and should be increased cautiously. In a pivotal clinical trial the dose averaged 9.3 ng per kg per min at Week 12. There is little experience with doses > 40 ng per kg per min, but higher doses have been utilized. At the end of a 1-year open-label trial, the average dose was 98 ng per kg per min. An absolute maximum dosage has not been established. With chronic use, it is expected that the dose will be increased if PAH symptoms persist, recur, or worsen; OR
- B) In children and adolescents, studies with Remodulin involving children and adolescents used similar dosing to that of adults. In a small (n = 13) analysis involving children and adolescents (mean age 11 years, range 3 to 17 years), the mean Remodulin dose at 12 months was 86 ng per kg per min. An absolute maximum dosage has not been established.

Initial Approval/Extended Approval.

- A) *Initial Approval:* Approve for 6 months.
- B) *Extended Approval:* Approve at 6-month intervals if the patient is benefiting from the agent as determined by the prescribing physician (e.g., improving in functional class or quality of life, or in other hemodynamic or clinical parameters).

Since PAH is a progressive disease, patients will deteriorate despite therapy.

Duration of Therapy in PAH. Indefinite in patients who are responding or benefiting as defined by the prescribing physician.

Labs/Diagnostics. The patient has had a right heart catheterization (with documented results) to confirm the proper diagnosis of WHO Group 1 PAH.

Other Uses with Supportive Evidence

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH):

Criteria. *The patient must meet the following criteria:* The agent is prescribed by, or in consultation with, a pulmonologist or a cardiologist.

Surgical pulmonary thromboendarterectomy (PTE) is the treatment of choice in symptomatic CTEPH.^{12,18-19} A prospective, uncontrolled observational cohort study analyzed the efficacy of long-term SC Remodulin in a difficult subset of inoperable CTEPH patients with severe symptoms (n = 25).¹³ Overall survival rates at 1, 2, 3 and 5 years were 80%, 80%, 80% and 53%, respectively, compared with untreated patients showing survival rates of 67%, 43%, 37%, and 16%, respectively (P = 0.02).¹³ Other data are available regarding use of Remodulin in CTEPH.¹⁴ The 4th World Symposium on Pulmonary Hypertension published a paper that focused on non-PAH forms of PH in 2009.¹² This paper notes in those with inoperable CTEPH, medical therapy may be appropriate, and patients should be considered

for enrollment in clinical trials. Preliminary data suggest that medications currently approved for PAH may have beneficial effects in patients with CTEPH, but as long as there are no robust data from randomized controlled trials, the decision of whether or not to treat CTEPH patients with these medications should be restricted to centers experienced in the management of the disease. If surgery is not possible, only limited options are available for patients with CTEPH.¹² The guidelines have not been updated since the approval of Adempas for CTEPH.²⁰ In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in CTEPH. *Dosing must meet the following:* The doses are titrated to efficacy and tolerability. The mean Remodulin dose is 28 ng per kg per minute as a continuous SC infusion.¹³⁻¹⁴ Dose ranges have been between 12.5 to 42 ng per kg per min SC. An absolute maximum dosage has not been established. Use of the intravenous route is permitted in cases where patients cannot use or tolerate the SC route of administration.

Initial Approval/Extended Approval.

- A) *Initial Approval:* Approve for 6 months.
- B) *Extended Approval:* Approve at 6-month intervals if the patient is benefiting from the agent as determined by the prescribing physician (e.g., improving in functional class or quality of life, improvement in the 6-minute walk distance, or in other hemodynamic or clinical parameters).

Duration of Therapy in CTEPH. Use is chronic, unless the patient undergoes pulmonary thromboendarterectomy or undergoes a lung transplantation.

Labs/Diagnostics. None required.

3. Patients who are Currently Receiving Remodulin (for any Indication). Approve a short-term supply of Remodulin for up to 14 days if the patient does not meet any of the criteria above or if there is insufficient information available. These cases should be forwarded immediately to the medical director for review. Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of Remodulin may have severe adverse consequences.

Abrupt withdrawal of Remodulin may lead to worsening of PAH symptoms and should be avoided.¹ In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Waste Management for All Indications.

The dose is weight-based and is titrated to efficacy and tolerability. The number of vials should be calculated based on the dose.

Conditions Not Recommended for Approval

Remodulin has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not recommended for Approval).

- 1. Chronic Obstructive Pulmonary Disease (COPD) in a Patient Without PAH (WHO Group 1).**
COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.¹⁵
- Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References	
	<ol style="list-style-type: none"> Remodulin injection [prescribing information]. Research Triangle Park, NC: United Therapeutic Corp.; October 2013. Simonneau G, Barst RJ, Nazzareno G, et al, for the treprostinil study group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. A double-blind, randomized, placebo-controlled trial. <i>Am J Respir Crit Care Med.</i> 2002;165:800-804. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. <i>Eur Respir J.</i> 2006;68:1195-1203. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. <i>CHEST.</i>

	<p>2006;129:1636-1643.</p> <ol style="list-style-type: none"> 5. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. <i>Am J Respir Crit Care Med.</i> 2005;172:1586-1589. 6. Benza RL, Rayburn BK, Tallaj JA, et al. Treprostinil-based therapy in the treatment of moderate-to-severe pulmonary arterial hypertension: long-term efficacy and combination with bosentan. <i>CHEST.</i> 2008;134:139-145. 7. Ivy DD, Claussen L, Doran A, et al. Transition of stable pediatric patients with pulmonary arterial hypertension from intravenous epoprostenol to intravenous treprostinil. <i>Am J Cardiol.</i> 2007;99(5):696-698. 8. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension. <i>CHEST.</i> 2006;129:683-688. 9. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. <i>J Am Coll Cardiol.</i> 2009;53:1573-1619. 10. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. <i>CHEST.</i> 2004;126:14-34. 11. Badesch DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. <i>CHEST.</i> 2007;131:1917-1928. 12. Hoeper MM, Barbera JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. <i>J Am Coll Cardiol.</i> 2009;54:S85-S95. 13. Skoro-Sajer N, Bonderman D, Wiesbauer F, et al. Treprostinil for severe inoperable chronic thromboembolic pulmonary hypertension. <i>J Thromb Haemost.</i> 2007;5(3):483-489. 14. Jensen KW, Kerr KM, Fedullo PF, et al. Pulmonary hypertensive medical therapy in chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy. <i>Circulation.</i> 2009;120:1248-1254. 15. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health, National Heart, Lung, and Blood Institute; Updated 2015. Available at: http://www.goldcopd.com. Accessed on July 7, 2015. 16. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. <i>J Am Coll Cardiol.</i> 2013;62(25 Suppl):D60-D72. 17. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. <i>J Am Coll Cardiol.</i> 2013;62(25 Suppl):D34-D41. 18. Hoeper MM, Madani MM, Nakanishi N, et al. Chronic thromboembolic pulmonary hypertension. <i>Lancet Respir Med.</i> 2014;2(7):573-582. 19. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. <i>J Am Coll Cardiol.</i> 2013;62:D92-D99. 20. Adempas® [prescribing information]. Whippany, NJ: Bayer; September 2014. 21. Mathier MA, McDevitt S, Saggarr R. Subcutaneous treprostinil in pulmonary arterial hypertension: practical considerations. <i>J Heart Lung Transplant.</i> 2010;29(11):1210-1217. 22. McLaughlin VV, Palevsky HI. Parenteral and inhaled prostanoid therapy in the treatment of pulmonary arterial hypertension. <i>Clin Chest Med.</i> 2013;34:825-840. 23. Safdar Z. Treatment of pulmonary arterial hypertension: the role of
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	prostacyclin and prostaglandin analogs. <i>Respir Med.</i> 2011;105(6):818-827. 24. Wilkens H, Lang I, Behr J, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): Updated recommendations of the Cologne Consensus Conference 2011. <i>Int J Cardiol.</i> 2011;154S:S54-S60.
CFR	
WAC	WAC 284-43-2050
RCW	
Contract Citation	<input checked="" type="checkbox"/> WAH
	<input checked="" type="checkbox"/> IMC
	<input checked="" type="checkbox"/> MA
Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM to PM	Cindy Bush
04/25/2018	Transferred to new template	Cindy Bush
06/08/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee

Appendix A: Classification of PAH

Guidelines from the ACCP for the screening, early detection, and diagnosis of PAH, established in 2004, recommend a right heart catheterization to confirm the presence of pulmonary hypertension, establish the diagnosis, and determine PAH severity.¹⁰ An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ATS and the Pulmonary Hypertension Association, notes all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to initiation of therapy.⁹ Also, the guidelines state that acute vasodilator testing should be done in all patients with idiopathic PAH who may be considered potential candidates for long-term therapy with oral calcium channel blockers. Idiopathic PAH patients in whom chronic calcium channel blocker therapy would not be considered, such as patients with overt right heart failure or hemodynamic instability, need not have acute vasodilator testing performed. The definition of an acute response that may suggest initiation with oral calcium channel blockers is a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output. Although this definition may misclassify a few patients who could be effectively treated with long-term oral calcium channel blockers, it will reliably identify those who are least likely to benefit from oral calcium channel blocker therapy and, therefore, provides the greatest degree of safety. Those with PAH due to conditions other than idiopathic PAH have a very low rate of long-term responsiveness to oral calcium channel blocker therapy and therefore, the decision to perform acute testing in these patients should be determined on an individual basis. Acute vasodilator testing is not indicated, and may be harmful, in those with significantly elevated left heart filling pressures.

The WHO categorizes PAH into stages. Also, five major categories of pulmonary hypertension are recognized. A summary of the stages (functional status) of PAH are provided in Table 1.

Table 1. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.¹⁰

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnea, fatigue, chest pain or presyncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is not discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increase by almost any physical activity.

WHO – World Health Organization.

Table 2 lists the updated clinical classification of pulmonary hypertension by the World Symposium on pulmonary hypertension.¹⁷

Table 2. Updated Classification of Pulmonary Hypertension.¹⁷

Group 1: Pulmonary Arterial Hypertension
Idiopathic
Heritable

<p>BMPR2 ALK-1, ENG, SMAD9, CAV1, KCNK3 Unknown Drug and toxin-induced Associated with Connective tissue disease Human immunodeficiency virus (HIV) infection Portal hypertension Congenital heart diseases Schistosomiasis Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis Persistent pulmonary hypertension of the newborn</p>
<p>Group 2: Pulmonary Hypertension Due to Left Heart Disease Left ventricular systolic dysfunction Left ventricular diastolic dysfunction Valvular disease Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</p>
<p>Group 3: Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia Chronic obstructive pulmonary disease Interstitial lung disease Other pulmonary diseases with mixed restrictive and obstructive pattern Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental lung diseases</p>
<p>Group 4: Chronic Thromboembolic Pulmonary Hypertension (CTEPH)</p>
<p>Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension.</p>

BMPR2 – Bone morphogenic protein receptor type 2; ALK-1 – Activin-like receptor kinase-1; ENG – Endoglin; Smad 9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.