



## Pulmonary Hypertension

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Pulmonary hypertension (PH) is high blood pressure in the blood vessels of the lungs. If the high blood pressure in the lungs is due to narrowing of the pulmonary arteries leading to increased pulmonary vascular resistance, it is known as pulmonary arterial hypertension (PAH). When the blood pressure inside the pulmonary vessels is high, the right side of the heart has to pump harder to move blood into the lungs to pick up oxygen. This can lead to failure of the right side of the heart. Patients with scleroderma are at increased risk for developing PH from several mechanisms. Frequently patients with scleroderma have multiple causes of their PH.

Patients who have limited cutaneous scleroderma (formerly known as CREST syndrome) are more likely to have PAH than those patients who have diffuse cutaneous systemic sclerosis. PAH may be the result of the same processes that cause damage to small blood vessels in the systemic circulation of patients with scleroderma. The lining cells of the blood vessels (endothelial cells) are injured and excessive connective tissue is laid down inside the blood vessel walls. The muscle that constricts the blood vessel may overgrow and narrow the blood vessel.

Other scleroderma patients may have PH because they have significant scarring (fibrosis) of their lungs. This reduces the blood oxygen level, which in turn, may cause a reflex increase in blood pressure in the pulmonary arteries.

### What are the Symptoms of Pulmonary Hypertension?

Patients with mild PH may have no symptoms. Patients with moderate or severe PH usually notice shortness of breath (dyspnea), especially

with exercise. Patients may also notice unusual chest pains and symptoms of right-sided heart failure, such as worsening shortness of breath and swelling of the feet and legs. Other symptoms that patients cite include a cough, lightheadedness or fainting, palpitations (heart racing or fluttering), and swelling.

### How is Pulmonary Hypertension Diagnosed?

In a patient with scleroderma, the development of unexplained shortness of breath should lead to consideration of possible PH.

A laboratory clue that a patient might have PH is a reduced diffusing capacity (DLCO) on pulmonary function tests (PFTs). The DLCO measures the ability of gas to move from the air, across the lung tissue and blood vessel wall, into the blood. In the absence of lung fibrosis, if the DLCO is less than 50 percent of its predicted value, this is a clue that PH may be present. Your provider might also order a blood test (called either BNP or nt-proBNP), which is a biomarker used to screen for and follow PH. Another test commonly used to screen patients for PH is the echocardiogram. It can estimate the pulmonary artery pressure fairly well in most patients in a noninvasive manner.

In order to confirm the presence of PH, a right heart catheterization is required to measure the actual pressure in the pulmonary arteries. This invasive test is done to more accurately measure the pressures in the lung blood vessels; to assess the blood flow generated by the heart (the cardiac output); to exclude an underlying leak or shunt contributing to the PH; to assess the function of the left side of the heart; and possibly to assess the patient's responsiveness to vasodilator therapy. The results of this test may

change the therapy prescribed by the physician. Right heart catheterization is the “gold standard” for diagnosing PAH and should always be done before being started on therapy.

An exercise test known as the six-minute walk test is often helpful in assessing exercise capacity in patients with PH. In addition, a Functional Class is often assigned to patients based on their activity tolerance, ranging from Class I to IV (with I being mildest and IV the most severe).

It is recommended that all patients with scleroderma should be screened annually for the presence of pulmonary hypertension.

## What is the Typical Course of PAH in Scleroderma?

It was previously thought that the development of PAH in patients with scleroderma was always associated with a poor prognosis. However, ongoing educational efforts regarding the risk of PAH in scleroderma has led to earlier diagnosis. Studies now suggest that patients identified with mild or early PAH will fare better if drug therapy is started before symptoms and exercise capacity worsen.

## What is the Treatment of PAH?

Supplemental oxygen and diuretics are often important parts of general treatment measures for PAH. If the oxygen level at rest, with exercise, or during sleep is low, supplemental oxygen therapy may be given. The decision to treat with anticoagulation is made on an individual basis by the patient and their physician, based on the potential risk of bleeding.

Calcium channel blockers (such as amlodipine, diltiazem or nifedipine) can help a small proportion of patients with PAH. Such treatment is successful in only a minority of scleroderma patients with PAH.

## PAH Specific Medications

The list of drugs for treating PAH continues to expand and include the following FDA-approved drugs: epoprostenol (generic, Flolan<sup>®</sup>, and Veletri<sup>®</sup>), treprostinil SQ or IV (Remodulin<sup>®</sup>), treprostinil inhaled (Tyvaso<sup>®</sup>), treprostinil oral (Orenitram<sup>®</sup>), iloprost (Ventavis<sup>®</sup>), bosentan (Tracleer<sup>®</sup>), ambrisentan (Letairis<sup>®</sup>),

macitentan (Opsumit<sup>®</sup>), sildenafil (generic, Revatio<sup>®</sup>), tadalafil (generic, Adcirca<sup>®</sup>), riociguat (Adempas<sup>®</sup>), and selexipag (Uptravi). Each of these drugs falls within one of three separate categories based on different mechanisms of action. These drugs are used alone or in combination with drugs in one or more other classes. Each will be briefly reviewed below.

## Prostacyclin Analogs

### Epoprostenol

Epoprostenol (generic, Flolan<sup>®</sup>, Veletri<sup>®</sup>) is a potent vasodilator that must be given by a constant intravenous infusion. This requires an indwelling central venous catheter and an infusion pump. In a multicenter, randomized, controlled clinical trial of chronic intravenous epoprostenol, in patients with PAH and scleroderma, there was improvement in exercise capacity and hemodynamics. A survival benefit was not seen in this population over the period of study, but the study was not designed to detect a difference in survival. Common side effects of epoprostenol therapy include headache, flushing, jaw pain with initial chewing, diarrhea, and bone pain. Other side effects include the potential for serious infection associated with the catheter. Chronic intravenous epoprostenol has been approved by the FDA for the treatment of patients in Functional Class III and IV PAH related to scleroderma.

### Treprostinil

Due to the complexity of chronic intravenous epoprostenol therapy, studies have since been undertaken with various analogues of prostacyclin being administered via the subcutaneous (under the skin), oral, and inhaled routes. Continuous subcutaneous infusion of treprostinil (Remodulin<sup>®</sup>) resulted in a slight improvement in exercise capacity, which was dose-related. The use of subcutaneous treprostinil may be limited by infusion site pain and redness. Treprostinil is approved for intravenous or subcutaneous delivery for the treatment of patients in Functional Class II, III, and IV PAH. Inhaled treprostinil (Tyvaso<sup>®</sup>), when administered four times daily, has been shown to improve exercise capacity in patients with Class III PAH. It is also approved for PH as a consequence of interstitial lung disease, which

is also common in patients with scleroderma. An oral form of treprostinil (Orenitram®) was approved by the FDA in December 2013.

### Iloprost

Iloprost (Ventavis®) is a prostacyclin analog delivered by inhalation 6–9 times daily that has been shown to improve a composite measure of exercise capacity and functional class. Inhaled iloprost has been studied in patients who remain symptomatic while on stable ERA (bosentan) therapy for at least three months. There was a borderline significant improvement in exercise capacity, and improvement in functional class. Combination therapy appeared to be safe and well tolerated. Inhaled iloprost has been approved by the FDA for treatment of patients with Functional Class III and IV PAH.

### Selexipag

Selexipag (Uptravi®) is an oral prostacyclin receptor agonist that has been shown to delay disease progression and reduce the risk of hospitalization for PAH. Side effects are similar to that of prostanoids and include headache, flushing, jaw pain, nausea, diarrhea, and bone pain

## Endothelin Receptor Antagonists (ERA)

### Bosentan

*Bosentan (Tracleer®)* is an oral endothelin receptor antagonist (ERA). In a pilot study, bosentan was shown to improve exercise capacity and cardio-pulmonary hemodynamics in patients with Functional Class III and IV PAH. A larger study confirmed improvement in exercise capacity and showed a reduction in clinical worsening. There is a potential for liver injury with bosentan, and monthly blood tests are required while receiving treatment. Bosentan is likely to produce major birth defects if used by pregnant women. Pregnancy must be prevented, and monthly pregnancy tests are required while taking bosentan.

### Ambrisentan

*Ambrisentan (Letairis®)*, like bosentan, is an FDA-approved ERA drug treatment for patients with PAH. To be taken once daily for patients in Functional Class II or III, this drug has shown improvement in exercise capacity. Similar to bosentan, ambrisentan should not be

taken by pregnant women, or women thinking of becoming pregnant. Other side effects may include edema and nasal congestion.

### Macitentan

*Macitentan (Opsumit®)* is the latest drug in the ERA class to be approved to treat PAH. Macitentan is approved for treatment of PAH to delay disease progression defined as death, initiation of intravenous (IV) or subcutaneous prostacyclin drugs, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). The need for PAH hospitalization was also reduced. Like other ERA drugs, macitentan is contraindicated in pregnancy because it may harm the developing fetus, and females of reproductive potential should be counseled on the use of reliable contraception and have a negative pregnancy test prior to initiating therapy and monthly thereafter.

## Phosphodiesterase-V (PDE-V) Inhibitors

### Sildenafil

*Sildenafil* was previously approved for the treatment of erectile dysfunction under the trade name of Viagra®. It is also approved for the treatment of PAH, under the trade name of Revatio® (a generic preparation is now also available). Sildenafil has been shown to improve exercise capacity, pulmonary artery pressure, and functional class in patients with PAH. Potential side effects include flushing, dyspepsia, visual changes, and nosebleeds.

### Tadalafil

*Tadalafil (Adcirca®)* is approved as a once-daily oral therapy for the treatment of PAH, and is indicated to improve exercise capacity in PAH patients. Side effects include headache, stomach upset, back pain, muscle pain, stuffy or congested nose, flushing, pain in arms or legs, or vision change.

## Guanylate Cyclase Stimulators

### Riociguat

*Riociguat (Adempas®)* is the first in a new class of drugs to be approved for treatment of PAH, including scleroderma patients with PAH, as well as for treatment of chronic thromboembolic pulmonary hypertension. Drugs in this new

class act to dilate blood vessels, thus reducing pulmonary vascular resistance and improving PAH. Riociguat has been shown to significantly improve exercise capacity, functional class, time to clinical worsening, and dyspnea score. Riociguat should not be used in pregnant women because it can harm the developing fetus.

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## Lung Transplantation

Lung transplantation may be an option for patients with severe PAH who do not respond to medical therapy. Due to the relatively high operative and perioperative risks, as well as the significant long-term risks of infection and rejection, lung transplantation should not be considered as first-line therapy or a cure for PAH. Not all patients are suitable candidates for lung transplantation. Gastro-esophageal reflux disease (GERD), or esophageal dysmotility occurs frequently in scleroderma, and may be a reason not to attempt lung transplantation due to the risk of aspiration.

## Putting it All Together

Pulmonary hypertension is not the only type of lung disease that can occur in patients with scleroderma. Interstitial lung disease (ILD), also called pulmonary fibrosis, is another potentially serious complication. Please contact the National Scleroderma Foundation for information on pulmonary fibrosis.

It is important to note that patients can have significant pulmonary involvement from their scleroderma before signs and symptoms appear. Therefore, it is important to have routine screening for possible pulmonary involvement, in particular pulmonary arterial hypertension and interstitial lung disease.

Due to the complexity of the diagnosis and treatment of scleroderma lung disease, strong consideration should be given to referral of patients to physicians with expertise in scleroderma, interstitial lung disease, and PH. This requires close collaboration between you, your rheumatologist, and your pulmonologist or cardiologist.

Please note that this brochure is provided for educational purposes only. It is not intended to substitute for informed medical advice.