Pulmonary Arterial Hypertension (PAH)

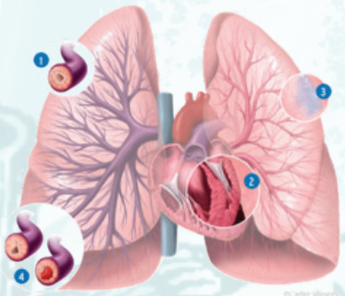
Pulmonary Hypertension Is Categorized into 5 Groups Based on Its Underlying Cause

Pre-capillary

WHO GROUP 1
PAH

WHO GROUP 3
PH associated with lung diseases and/or hypoxia

WHO GROUP 4
Chronic thromboembolic pulmonary hypertension (CTEPH)



Post-capillary

WHO GROUP 2
PH associated with left heart disease

WHO GROUP 5:
Pulmonary hypertension with unclear and/or multifactorial mechanisms

Who Has PAH?

Studies from Scotland and France revealed a prevalence ranging from

5-52 CASES PER MILLION ADULTS

Overall PAH female to male ratio 4.1:1 VS

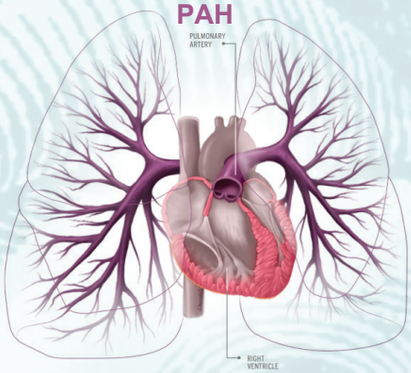
Most common age of patients with PAH BETWEEN **45-54** YEARS OLD

2.8 YEARS — Mean time from Symptom onset → Diagnostic catheterization

61.2% 5-year survival

Pulmonary Arterial Hypertension – WHO Group 1

Pulmonary arterial hypertension (PAH) is a rare, severe disease that affects the heart's ability to pump blood to the lungs and worsens over time.



Vasoactive Pathways in PAH

Blood vessel endothelium secretes chemical mediators to regulate vascular tone, blood pressure, and local blood flow

- **NITRIC OXIDE PATHWAY** — Under expressed in PAH
- **PROSTACYCLIN PATHWAY** — Under expressed in PAH
- **ENDOTHELIN PATHWAY** — Over expressed in PAH

Clinical Classifications of PAH

IDIOPATHIC | **HERITABLE** | **DRUG- AND TOXIN-INDUCED** | **ASSOCIATED**

Patients with certain types of PAH can have worse prognoses than others (eg, CTD-associated vs idiopathic, respectively)

Patients Present With Nonspecific Symptoms, Requiring Vigilance for Timely Diagnosis

Symptom onset ···>2 years···➤ Diagnosis

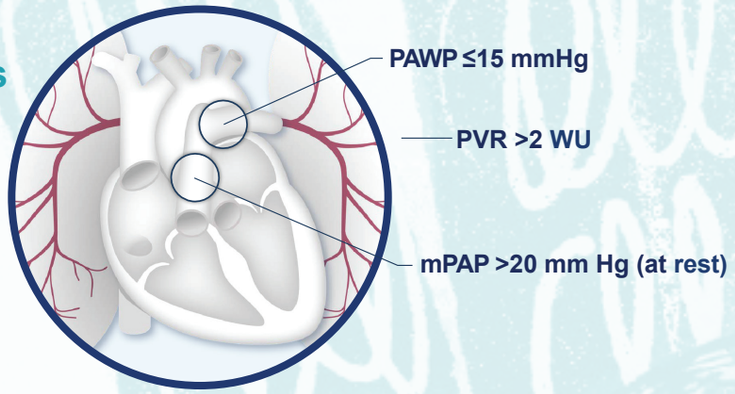
- **Dyspnea on exertion or at rest**
- **Fatigue**
- **Dizziness and/or syncope**
- **Angina**
- **Lower extremity edema**

Delayed diagnosis is common but detrimental; early recognition of symptoms and timely action, including early referral to a PH Expert Center, are important for patient outcomes

Pulmonary Arterial Hypertension (PAH) - continued

Right Heart Catheterization Is Required for Definitive Diagnosis

Diagnostic criteria of PAH according to RHC



What is Risk Assessment?

- Risk assessment enables healthcare providers to see a fuller picture of PAH severity by combining individual test results into a single "risk status"— high, intermediate, or low risk.
- Formal risk calculations can help healthcare providers determine a patient's predicted 5-year survival rate.
- In multiple registries involving thousands of patients with PAH, **those who achieve low-risk status, particularly in their first year after diagnosis, have a better likelihood of survival.** Therefore, treating to a goal of low-risk status can help give a patient a better long-term prognosis.

	Intermediate risk		
Low risk	Intermediate-low risk	Intermediate-high risk	High risk

Common Tests Used as Part of Risk Assessment

6-minute walk test

During a risk assessment, the HCP will measure how far the patient is able to walk in 6 minutes. This 6-minute walk test gives clues about how the heart, lungs, and blood vessels are doing.

NT-proBNP/BNP

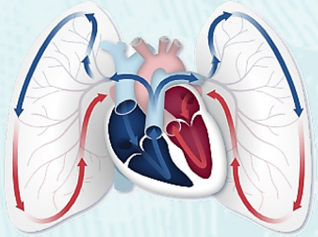
PAH can cause the heart to work harder than normal, which releases high levels of a hormone NT-proBNP/BNP. When levels are high, the heart is under more strain than normal.

Functional Class

Functional Class is a predictor of life expectancy. FC evaluation consists of 4 categories based on the symptoms a patient experiences when doing everyday activities.

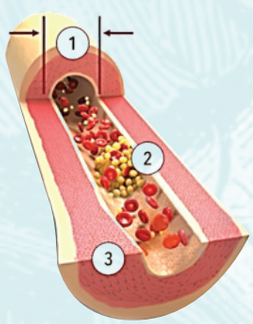
Other Tests Used as Part of Risk Assessment

- **Pulmonary Function Test (PFT)**
- **Right Heart Catheterization (RHC)**
- **Chest x-rays**
- **Echocardiogram (Echo)**



Treprostinil MOA

Treprostinil is a prostacyclin-class therapy with a mechanism of action that targets 3 of the major pathologic changes that occur in PAH.



1. Vasoconstriction
2. Platelet aggregation
3. Smooth muscle proliferation

Remodulin

Indication

Remodulin is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to diminish symptoms associated with exercise

- Remodulin is delivered through a pump system for continuous delivery of medicine 24 hours a day, 7 days a week
- Remodulin patients are taught by a specialty pharmacy how to mix and/or manage their therapy
- Remodulin is initiated at a low dose (weight-based) and adjusted to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin
- No maximum or set dose
- Excessive pharmacologic effects include headache, nausea, vomiting, restlessness, anxiety, infusion site pain/reaction
- Patients are warned to avoid abrupt cessation of infusion or sudden large reductions in dose

When Is It Time for Parenteral Therapy?

HIGH RISK per key indicators[3-6]

WORSENING DISEASE despite treatment[3-6]

INADEQUATE CLINICAL RESPONSE to current treatment[3-6]

THE GUIDELINES AGREE: CONSIDER PARENTERAL THERAPY

2009	2014	2015	2018
ACCF/AHA Consensus[3]	CHEST Treatment Recommendations[4]	ESC/ERS Treatment Guidelines[5]	6th World Symposium[7]

According to the 2022 ESC/ERS Guidelines, patients who are at high risk at baseline-and intermediate-high or high risk at follow up, should be considered for treatment with parenteral prostacyclin

Remodulin Administration Routes

SC

- Continuous infusion
- Preferred administration route
- No surgery required
- Several SC catheter options

IV

- Continuous infusion
- CVC placed by interventional radiology or vascular surgery
- CVC tunneled under the skin
- Single lumen CVC recommended for prostacyclin administration
- Several distinct CVC types

Remodulin - continued

Pump Options for Subcutaneous Delivery of Remodulin

REMUNITY® PUMP FOR REMODULIN® (treprostinil) Injection

- Administration up to 72 hours per cassette (up to 3mL)
- Patient-filled cassettes or the option of SP filled
- Audible and vibration alarms
- Water-resistant to a depth of 8 ft for 30 min or 12 ft for 3 min
- Separate, wireless remote
- Small and discreet
- Rechargeable batteries
- Designed specially for PAH
- For use with Remodulin only

Pump Options for Intravenous Delivery of Remodulin

CADD®

SOLIS AMBULATORY INFUSION PUMP FOR PATIENTS STARTING OR CONTINUING IV THERAPY WITH REMODULIN

- Lower extremity edema

Orenitram Overview

Indication

Orenitram is a prostacyclin mimetic indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to delay disease progression and to improve exercise capacity

Strengths

Available in 5 tablet strengths

Tablets not shown at actual size.

Dosing Simplified

Each day, patients will know their dose of Orenitram as they continue up-titrating to their target dose

Confident Start

An all-in-one kit that outlines the first 3 months of 0.125 mg TID dosing and titration

orenitram® treprostinil
EXTENDED-RELEASE TABLETS

Orenitram

- Orenitram provides the ability to titrate the dose up or down to tolerability and clinical response*
  - Target dose ≥ 9mg daily (> 3mg 3x per day, every 8 hours)
- Considered for PAH patients:
  - With intermediate-risk parameters who are not meeting individual goals with adequate time to titrate
    - For patients requiring a faster titration, a transition from Remodulin may be appropriate
  - Who are not appropriate for or have refused parenteral therapy
  - Who are clinically stable on parenteral therapy and are appropriate to transition to oral (pill) medication
- Patients should not skip doses or abruptly discontinue therapy without talking to their provider
- Expected AEs include headache, nausea, diarrhea and vomiting
  - Mitigation strategies may be helpful

Take Orenitram with food

Swallow Orenitram tablets whole

Do not split, break, crush, or chew before swallowing

*Maximum daily dose 120mg

Tyvaso for PAH Overview

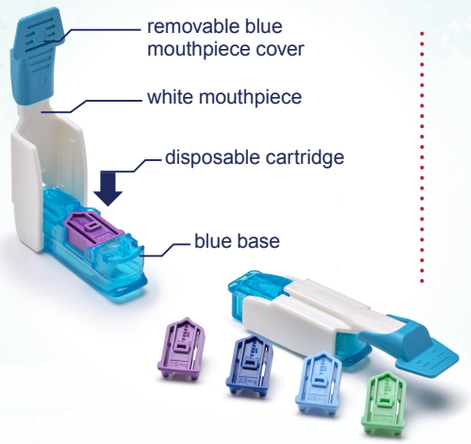
Indications

Tyvaso is a prostacyclin mimetic indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability

TYVASO DPI (treprostinil) INHALATION POWDER

TYVASO (treprostinil) INHALATION SOLUTION



TD-300 Features

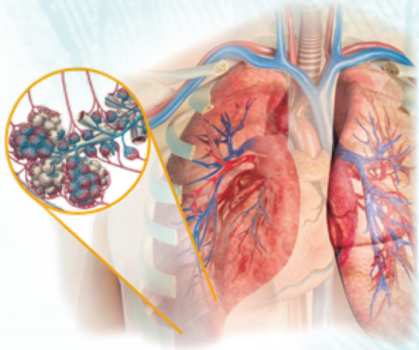
Mode Switch
Allows patient to "Program the number of breaths prescribed then "Run" treatment administration.

Full-Color Display
Provides informative prompts to help patients administer their medication.

Multifunction Button
Includes just 1 button for all important device functions (ie,power, start, pause).

Internal Battery
Offers all-day cordless use after 8-hour overnight charging via wall plug.

How Tyvaso Works



- Direct-to-lung delivery results in higher concentrations in the pulmonary arterial vasculature, which may selectively enhance blood flow for better ventilation and perfusion matching with less off-target exposure.

EASY – EFFICACY and SAFETY – EARLY

- TYVASO provides **EASY**-to-use prostacyclin delivery with proven **EFFICACY** and **SAFETY** – an option for appropriate patients identified **EARLY**, including those who:
  - Are at low and intermediate-low risk
  - Are on mono or dual background therapy
  - Have systemic tolerability concerns
- Expected AEs include cough, headache and throat irritation

Tyvaso Device Choice – Tyvaso Administration Routes

Administered direct-to-lung via nebulizer or dry powder inhaler (DPI)

TYVASO DPI (treprostinil) INHALATION POWDER

- Small, portable dry powder inhaler that fits in the palm of your hand
- Insert single-dose cartridge and inhale 1 breath
  - Replace inhaler every 7 days
- 4x daily; Each dose is inhaled in less than 2 seconds
- Increase cartridge strength by 16 mcg per session every 1-2 weeks to a target maintenance dose of 48 mcg to 64 mcg

TYVASO (treprostinil) INHALATION SOLUTION **Nebulizer**

- Handheld nebulizer that can be charged overnight for cordless flexibility
- Set up device 1x each morning
  - Clean device 1x each night
- 4x daily; Each treatment session only takes 2-3 minutes
- Increase by 3 breaths per session every 1-2 weeks to a target maintenance dose of 9-12 breaths

What is PH-ILD?

- **PH (Pulmonary Hypertension)**
  - Pulmonary Hypertension = high blood pressure in the lungs
- **ILD (Interstitial Lung Disease)**
  - Interstitial Lung Disease is a group of serious, progressive lung disorders that can damage the lungs and make it harder to breathe
- **Some patients with ILD can also have PH, which is why you see the terms put together as one**
  - PH associated with Interstitial Lung Disease is referred to as PH-ILD
- **When present with ILD, PH significantly increases morbidity and mortality**

Definition of WHO Group 3 PH

- Hemodynamic parameters for Group 3 PH:
  - **Group 3 PH is differentiated from Group 1 PAH through diagnostic testing revealing significant lung disease**

PAWP ≤15 mmHg + **mPAP >20 mmHg** + **PVR ≥3 Wood units** → **PH Diagnosis Hemodynamic Definition**

ILD Symptoms Can Mask the Symptoms of PH-ILD

Symptoms of PH-ILD	Symptoms that overlap with ILD
• Increased exertional dyspnea • Fatigue • Cough • Light-headedness • Palpitations • Lower extremities edema • Chest pain	• Increased exertional dyspnea • Fatigue • Cough

PH-ILD can be difficult to predict accurately with examinations.

By the time physical signs are visible, it is most often late-stage PH.

Diagnostic Testing for PH in ILD

Right Heart Catheterization

- Considered the gold standard for PH diagnosis and assessment
- Invasive procedure during which a specialized catheter is passed through the right heart and into the pulmonary arterial system

Imaging:

- **X-ray**
- **CT Scan**
- **TTE**

Diagnostic Testing:

- **BNP/NT-proBNP**

Pulmonary Function Tests

- **Spirometry**
- **Plethysmography**
- **Pulse oximetry**
- **Arterial blood gases**
- **Diffusion of the lungs for carbon monoxide (DLCO)**

Average 6MWT Results

- Healthy adult: 571 ± 40 meters
- Adult with PH: 366 ± 126 meters
- Distance <345 meters is independent risk factor for PH

6-minute Walk Test

- Submaximal exercise test to assess aerobic capacity and endurance
- Measures distance an individual can cover over 6 minutes
- In evaluation of PH in ILD, pulse oximetry is used to measure exercise-induced oxygen desaturation
- Findings suggestive of PH include:
  - Desaturation to <88% when disproportionate to extent of underlying ILD
  - Decreased distance
  - High dyspnea scores
- Can be used to measure response to treatment and as a predictor of mortality

Tyvaso for PH-ILD

TYVASO DPI (treprostinil) INHALATION POWDER

TYVASO (treprostinil) INHALATION SOLUTION

- **TYVASO** is the first and only FDA-approved medication to treat PH-ILD.
- **TYVASO** and **TYVASO DPI** are inhaled prostacyclin mimetics indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

Tyvaso Device Choice – Tyvaso Administration Routes

Administered direct-to-lung via nebulizer or dry powder inhaler (DPI)

TYVASO DPI (treprostinil) INHALATION POWDER

- Small, portable dry powder inhaler that fits in the palm of your hand
- Insert single-dose cartridge and inhale 1 breath
  - Replace inhaler every 7 days
- 4x daily; Each dose is inhaled in less than 2 seconds
- Increase cartridge strength by 16 mcg per session every 1-2 weeks to a target maintenance dose of 48 mcg to 64 mcg

TYVASO (treprostinil) INHALATION SOLUTION **Nebulizer**

- Handheld nebulizer that can be charged overnight for cordless flexibility
- Set up device 1x each morning
  - Clean device each night
- 4x daily; Each treatment session only takes 2-3 minutes
- Increase by 3 breaths per session every 1-2 weeks to a target maintenance dose of 9-12 breaths
- For PH-ILD patient: Increase by 1 breath per sesson every 1-2 weeks, as tolerated

How to Take Tyvaso: PH-ILD

ONCE DAILY SETUP

Convenient once-daily setup

Compared with other nebulizer systems

~2-3 SETUP

Each treatment session only takes approximately 2-3 minutes

Cordless flexibility

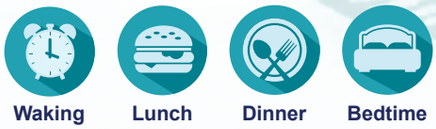
EASY – EFFICACY and SAFETY – EARLY

- TYVASO provides **EASY**-to-use prostacyclin delivery with proven **EFFICACY** and **SAFETY** – an option for appropriate patients identified **EARLY**, including those who:
  - Are at low and intermediate-low risk
  - Are on mono or dual background therapy
  - Have systemic tolerability concerns
- Expected AEs include cough, headache and throat irritation

How to Take Tyvaso DPI: PH-ILD

Single-dose cartridges, prefilled with medicine

1 breath per cartridge, 4x daily



Recommended Dosing & Titration for PH-ILD

STARTING DOSE
1 breath per cartridge/ 4x daily

16 mcg

Increase cartridge strength every 1-2 weeks as tolerated

16 mcg → 32 mcg → 48 mcg → 64 mcg

TARGET DOSE
1 breath per cartridge/ 4x daily

48 mcg TO 64 mcg

Recommended Dosing & Titration for PH-ILD

STARTING DOSE
3 breaths/ 4x daily

Add 1 breath per session every week

TARGET DOSE
9-12 breaths/ 4x daily

WEEK 1 → WEEK 8

Most people who received TYVASO in the clinical study had reached the target dose by week 8

Treatment sessions can be scheduled around daily activities, approximately every 4 waking hours