NEW DRUG APPROVAL

Brand Name	Tyvaso DPI™
Generic Name	treprostinil
Drug Manufacturer	United Therapeutics Corporation

New Drug Approval

FDA approval date: May 23, 2022

Review designation: Priority; Orphan

Type of review: Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 214324

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Pulmonary arterial hypertension (PAH): It is a progressive condition characterized by elevated pulmonary arterial pressures leading to right ventricular (RV) failure. The pulmoary vascular injury underlying PAH occurs in an idiopathic form or in association with other disease states or exposures and is probably a final common response to environmental or disease-related inciting factors coupled with genetically determined susceptibilities. Treatment options have expanded over the last decade and now include 6 U.S. Food and Drug Administration–approved medications; with these advances, prognosis is improving. This review de-scribes the current classification system for PAH, new insights into its pathogenesis and prognosis, a recent treatment algorithm, and potential future therapeutic targets.

Pulmonary hypertension associated with interstitial lung disease (PH-ILD): Interstitial lung diseases are a distinct type of chronic respiratory disorder that can result in pulmonary hypertension. There are numerous causes of ILD but all are characterized by dyspnea and abnormal lung function, with arterial oxygen desaturation occurring as the disease advances. Patients with idiopathic pulmonary fibrosis (IPF), a relentlessly progressive form of ILD, are particularly likely to develop pulmonary hypertension. Both chronic hypoxemia with subsequent pulmonary vasoconstriction and obliteration of the pulmonary vascular bed as a result of interstitial fibrosis have traditionally been considered the pathways by which pulmonary hypertension develops in ILD. Sarcoidosis, pulmonary Langerhans cell histiocytosis (PLCH), and lymphangioleiomyomatosis (LAM) are types of ILD that may directly involve the pulmonary vasculature, in addition to causing interstitial fibrosis. Collagen vascular diseases such as scleroderma may cause pulmonary hypertension as a result of progressive ILD or by direct pulmonary vascular involvement.

Epidemiology: PAH is rare. It makes up about 5% of pulmonary hypertension (PH) cases.

- 2–7.6 cases per million adults/year
- 10.6–26 cases per million adults
- Affects all races/ethnicities, sexes, and ages; however:
  - Mean age at diagnosis: 50 ± 14 years
  - Women: 4x higher risk

Patients with connective tissue diseases or who have a history of methamphetamine use are at greatest risk for developing PAH. Advanced lung disease such as ILD or COPD are 2 key risk factors for developing PH.

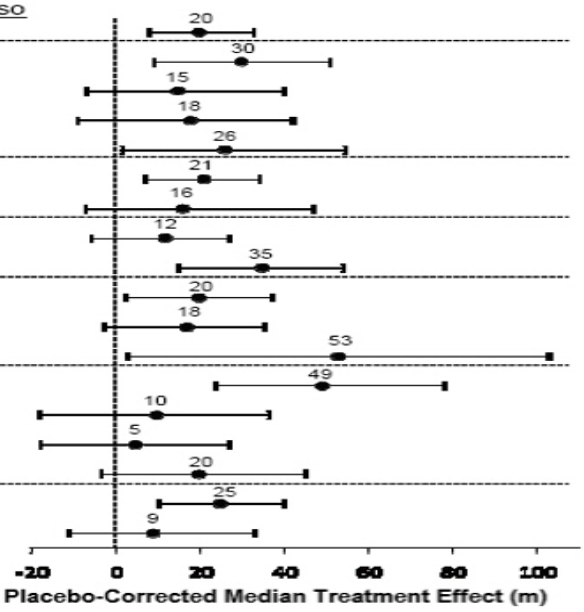
The exact cause of PAH is unknown, but the condition affects about 45,000 U.S. patients and occurs 3–5 times more frequently in females than males. Interstitial lung disease (ILD) is a group of diseases characterized by marked scarring or fibrosis of the lungs. PH-ILD affects about 30,000 U.S. patients and shares many of the same symptoms as PAH.

Efficacy

Pulmonary Arterial Hypertension (WHO Group 1): TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled, multicenter study of patients with PAH (NCT00147199). The study population included 235 clinically stable subjects with PAH (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least 3 months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso™ Inhalation Solution in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominately female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

Figure 1: Placebo-Corrected Median Treatment Effect (Hodges-Lehmann Estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso™ Inhalation Solution for Various

		Sample Size Placebo	Tyvaso
Overall	All Subjects	120	115
Age (quartile)	18–45 yrs	39	20
	46–54 yrs	25	30
	55–63 yrs	27	36
	64–75 yrs	29	29
Gender	Female	98	93
	Male	22	22
Geographic region	North America	72	70
	Rest Of World	48	45
Etiology	Idiopathic/Heritable	67	64
	Connective tissue diseases	37	40
	Other	16	11
Baseline 6MWD (quartile)	204–300 m	30	29
	303–359 m	29	30
	360–401 m	25	33
	402–450 m	36	23
Background therapy	Bosentan	88	77
	Sildenafil	32	38



The primary efficacy endpoint of the trial was the change in 6MWD relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3 to 5 hours after bosentan or 0.5 to 2 hours after sildenafil. Patients receiving Tyvaso™ Inhalation Solution had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values. 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy.

Long-term Treatment of PAH: In long-term follow-up of patients who were treated with Tyvaso™ Inhalation Solution in the pivotal study and the open-label extension (N=206) (NCT00147199), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. These uncontrolled observations do not allow comparison with a control group not given Tyvaso™ Inhalation Solution and cannot be used to determine the long-term effect of Tyvaso™ Inhalation Solution on mortality.

Pulmonary Hypertension Associated with ILD (WHO Group 3): INCREASE was a 16-week, randomized, double-blind, placebo-controlled, multicenter study that enrolled 326 patients with PH-ILD (NCT02630316). Enrolled study patients predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.

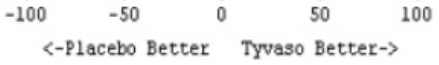
Patients in the INCREASE study were randomized (1:1) to either placebo or Tyvaso™ Inhalation Solution in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the course of the 16-week study. Approximately 75% of patients randomized to Tyvaso™ Inhalation Solution titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to Tyvaso™ Inhalation Solution reaching a dose of 12 breaths, 4 times daily during the study.

The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Patients receiving Tyvaso™ Inhalation Solution had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 (p=0.004) using Hodges-Lehmann estimate.

The treatment effect on 6MWD at Week 16 was consistent for various subgroups, including etiology of PH-ILD, disease severity, age, sex, baseline hemodynamics, and dose in below screenshot.

Figure 2: Forest Plot on Subgroup Analyses of Peak 6MWD (Meter) at Week 16 (PH-ILD)

Subgroup	Tyvaso # of Patients	Placebo # of Patients	H-L Estimate (95% CI)	p-value
Overall	163	163	21.0(7.0, 37.0)	0.0043
Age Group				
<65 years old	64	48	11.0(-11.0, 46.0)	0.3203
65 - <80 years old	83	100	27.0(7.0, 46.0)	0.0111
>=80 years old	16	15	19.5(-38.0, 74.0)	0.9457
Sex				
Male	78	95	8.0(-12.0, 30.0)	0.4877
Female	85	68	34.0(12.0, 57.0)	0.0010
Baseline 6MWD Category				
<=350 meters	136	133	24.0(6.0, 41.0)	0.0084
>350 meters	27	30	16.0(-16.0, 47.0)	0.2697
PH-ILD Etiology				
IIP	65	81	32.0(12.0, 55.0)	0.0030
CPFE	42	40	2.0(-28.0, 32.0)	0.8742
CTD	40	32	39.0(3.0, 78.0)	0.0317
Other	16	10	0.0(-89.0, 54.0)	0.3607
Baseline PVR Category				
<4 WU	32	34	-3.0(-26.0, 26.0)	0.7345
>=4 WU	131	129	28.0(11.0, 46.0)	0.0019
Maximum Study Drug Dose				
4-6 breaths	6	2	-16.5(-62.0, 29.0)	0.8481
7-9 breaths	37	24	18.0(-8.0, 43.0)	0.2875
>=10 breaths	78	94	30.0(14.0, 48.0)	0.0006



Time to clinical worsening in the INCREASE study was defined as the time of randomization until 1 of the following criteria were met: hospitalization due to a cardiopulmonary indication, decrease in 6MWD >15% from baseline directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation. Treatment with Tyvaso™ Inhalation Solution in patients with PH-ILD resulted in numerically fewer hospitalizations. The numbers of reported deaths were the same for both treatment groups (Table 1). Overall, treatment with Tyvaso™ Inhalation Solution demonstrated a statistically significant increase in the time to first clinical worsening event (log-rank test p=0.041;), and a 39% overall reduction in the risk of a clinical worsening event (HR=0.61 [95% CI; 0.40, 0.92].

Table1: Clinical Worsening Events (PH-ILD)

		Tyvaso™ Inhalation Solution n=163 n (%)	Placebo n=163 n (%)	HR (95% CI)
Clinical worsening		37 (22.7%)	54 (33.1%)	0.61 (0.40, 0.92)
First contributing event	Hospitalization due to a cardiopulmonary indication	18 (11.0%)	24 (14.7%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	13 (8.0%)	26 (16.0%)	
	Death (all causes)	4 (2.5%)	4 (2.5%)	
	Lung transplantation	2 (1.2%)	0	
First of each event	Hospitalization due to a cardiopulmonary indication	21 (12.9%)	30 (18.4%)	
	Decrease in 6MWD >15% from baseline directly related to PH-ILD	16 (9.8%)	31 (19.0%)	
	Death (all causes)	8 (4.9%)	10 (6.1%)	
	Lung transplantation	2 (1.2%)	1 (0.6%)	

Safety

ADVERSE EVENTS

Pulmonary Arterial Hypertension:

(Tyvaso DPI™): The most commonly reported adverse events on Tyvaso DPI™ during the 3-week treatment phase included cough, headache, dyspnea, and nausea. Patient tolerability, as assessed by incidence of new adverse events following transition to Tyvaso DPI™, was consistent with the expected known safety profile of Tyvaso™ Inhalation Solution. Below table lists the adverse events that occurred at a rate of at least 4%.

Table 2: Adverse Events in ≥4% of PAH Patients Receiving Tyvaso DPI™ in BREEZE (Treatment Phase)

Adverse Event	Tyvaso DPI™ (n=51) n (%)
Cough	18 (35.3)
Headache	8 (15.7)

Dyspnea	4 (7.8)
Nausea	3 (5.9)

(Tyvaso™ Inhalation Solution): The most commonly reported adverse reactions on Tyvaso™ included cough and throat irritation, headache, gastrointestinal effects, muscle, jaw or bone pain, dizziness, flushing, and syncope. Table 3 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with Tyvaso™ than with placebo

Table 3: Adverse Events in ⩾4% of PAH Patients Receiving Tyvaso™ Inhalation Solution and More Frequent* than Placebo in TRIUMPH I

Adverse Event	**Treatment n (%)**	
	Tyvaso™ Inhalation Solution n=115	**Placebo n=120**
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	27 (23)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

*More than 3% greater than placebo

Pulmonary Hypertension Associated with ILD: In a 16-week, placebo-controlled study (INCREASE) of 326 patients with PH-ILD (WHO Group 3), adverse reactions on Tyvaso™ Inhalation Solution were similar to the experience in studies of PAH.

WARNINGS & PRECAUTIONS

Risk of Symptomatic Hypotension: Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with Tyvaso DPI™ may produce symptomatic hypotension.

Risk of Bleeding: Tyvaso DPI™ inhibits platelet aggregation and increases the risk of bleeding.

Effect of Other Drugs on treprostinil: Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

Bronchospasm: Like other inhaled prostaglandins, Tyvaso DPI™ may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with Tyvaso DPI™.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

Dose & Administration

ADULTS

- Initial dosage: one 16 mcg cartridge per treatment session.
- Dosage should be increased by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals, if tolerated.
- Titrate to target maintenance doses of 48 mcg to 64 mcg per treatment session, 4 times daily.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Inhalation powder: Single-dose plastic cartridges containing 16, 32, 48, or 64 mcg of treprostinil as a dry powder formulation