



UNITED THERAPEUTICS ANNOUNCES FDA APPROVAL OF TYVASO DPI™

First approval of a dry powder inhaler for treatment of PAH and PH-ILD

DPI device represents a convenient option for administration of treprostinil therapy

Commercial launch activities underway; patient availability expected in June 2022

SILVER SPRING, Md., and RESEARCH TRIANGLE PARK, N.C., May 24, 2022 – United Therapeutics Corporation (**Nasdaq: UTHR**), a public benefit corporation, announced today that the U.S. Food and Drug Administration (**FDA**) has approved Tyvaso DPI™ (treprostinil) inhalation powder for the treatment of pulmonary arterial hypertension (**PAH**; WHO Group 1) and pulmonary hypertension associated with interstitial lung disease (**PH-ILD**; WHO Group 3) to improve exercise ability. Tyvaso DPI represents a new formulation and inhalation device for inhaled treprostinil and is the only dry powder inhaler approved by the FDA for use in PAH and PH-ILD.

“Tyvaso DPI is one of the easiest ways for patients to administer a prostacyclin, delivering the proven efficacy of treprostinil through a small inhaler that fits in the palm of the patient’s hand,” said **Michael Benkowitz**, President and Chief Operating Officer of United Therapeutics. “We look forward to launching this exciting new product, and the opportunity to introduce treprostinil to more patients with PAH and PH-ILD.”

“Prostacyclin-based therapies are effective in treating PAH, and recent data from the *INCREASE* study has shown that inhaled treprostinil is an effective treatment for PH-ILD,” said **Shelley Shapiro, M.D., Ph.D.** at the David Geffen UCLA School of Medicine Pulmonary Hypertension Program. “The convenience and portability of Tyvaso DPI may make it an important new option for patients with WHO Group 1 PAH and with WHO Group 3 PH-ILD, with the potential for improving the quality of life for this patient population.”

PAH is life-threatening high blood pressure in the arteries of the lungs, affecting the ability of the heart and lungs to work properly. PAH affects an estimated 45,000 patients in the United States. Interstitial lung disease (**ILD**) is a group of conditions in which marked scarring occurs within the lungs. It is often complicated by pulmonary hypertension (**PH**; high blood pressure in the lungs), which furthers symptoms and decreases survival. PH is estimated to affect at least 15% of patients with early-stage ILD (approximately 30,000 PH-ILD patients in the United States) and may affect up to 86% of patients with more severe ILD. Tyvaso® (treprostinil) Inhalation Solution and Tyvaso DPI are the only therapies approved by the FDA to treat PH-ILD.

FDA approval of the new drug application for Tyvaso DPI is supported by data from *BREEZE*, an open label study of 51 PAH patients on a stable regimen of Tyvaso Inhalation Solution who were transitioned to Tyvaso DPI. In subjects with PAH, transition from Tyvaso Inhalation Solution to Tyvaso DPI demonstrated safety and tolerance during the three-week treatment phase with significant improvements in six-minute walk distance, device preference and satisfaction, and patient reported outcomes. Top line data from *BREEZE* were issued in [January 2021](#), efficacy data were presented in [September 2021](#), long-term open-label safety data were published in [April 2022](#), and additional long-term safety and efficacy data were presented in [May 2022](#). **See the Important Safety Information below under “About Tyvaso DPI”.**

About PAH

Also known as World Health Organization (**WHO**) Group 1 Pulmonary Hypertension, PAH is life-threatening high blood pressure in the arteries of the lungs, affecting the ability of the heart and lungs to work properly in afflicted patients. PAH is a serious, progressive disease for which there is no known cure. PAH affects an estimated 45,000 patients in the United States.

About PH-ILD

Interstitial lung disease is a group of lung diseases that are characterized by marked scarring or fibrosis of the bronchioles and alveolar sacs within the lungs. Increased fibrotic tissue in ILD prevents oxygenation and free gas exchange between the pulmonary capillaries and alveolar sacs, and the condition can present with a wide range of symptoms, including shortness of breath with activity, labored breathing, and fatigue. Pulmonary hypertension frequently complicates the course of patients with ILD and is associated with worse functional status measured by exercise capacity, greater supplemental oxygen needs, decreased quality of life, and worse outcomes.

PH-ILD is estimated to affect at least 15% of patients with ILD (approximately 30,000 PH-ILD patients) and may affect up to 86% of patients with more severe ILD. PH-ILD is included within Group 3 of the WHO classification of PH.

About TYVASO® (treprostinil) Inhalation Solution and TYVASO DPI™ (treprostinil) Inhalation Powder

Eyebrow (abbreviated) Indication

- For the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability.
- For the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.

INDICATION

TYVASO (treprostinil) Inhalation Solution and TYVASO DPI (treprostinil) Inhalation Powder are prostacyclin mimetics indicated for the treatment of:

- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with TYVASO establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all clinical experience with inhaled treprostinil has been on a background of an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor. The controlled clinical experience with TYVASO was limited to 12 weeks in duration.

- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study with TYVASO establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- TYVASO and TYVASO DPI are pulmonary and systemic vasodilators. In patients with low systemic arterial pressure, either product may produce symptomatic hypotension.
- Both products inhibit platelet aggregation and increase the risk of bleeding.
- Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} 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.

- Like other inhaled prostaglandins, TYVASO and 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 and TYVASO DPI.

DRUG INTERACTIONS/SPECIFIC POPULATIONS

- The concomitant use of either product with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension.
- Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor, gemfibrozil, increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer, rifampin, decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8.
- Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality. There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.
- Safety and effectiveness in pediatric patients have not been established.
- Across clinical studies used to establish the effectiveness of TYVASO in patients with PAH and PH-ILD, 268 (47.8%) patients aged 65 years and over were enrolled. The treatment effects and safety profile observed in geriatric patients were similar to younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

ADVERSE REACTIONS

- Pulmonary Arterial Hypertension (WHO Group 1)

In a 12-week, placebo-controlled study (*TRIUMPH I*) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most common adverse reactions seen with TYVASO in $\geq 4\%$ of PAH patients and more than 3% greater than placebo were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%). In addition, adverse reactions occurring in $\geq 4\%$ of patients were dizziness and diarrhea.

In a 3-week, open-label, single-sequence, safety and tolerability study (*BREEZE*) conducted in 51 patients on stable doses of TYVASO who switched to a corresponding dose of TYVASO DPI, the most commonly reported adverse events seen with TYVASO DPI in $\geq 4\%$ of PAH patients during the 3-week treatment phase included cough (35.3%), headache (15.7%), dyspnea (7.8%), and nausea (5.9%).

- Pulmonary Hypertension Associated with ILD (WHO Group 3)

In a 16-week, placebo-controlled study (*INCREASE*) of 326 patients with PH-ILD (WHO Group 3), adverse reactions with TYVASO were similar to the experience in studies of PAH.

Please see Full Prescribing Information for [TYVASO](#) or [TYVASO DPI](#), Instructions for Use manuals for [TD-100 and TD-300](#) TYVASO® Inhalation System and [TYVASO DPI™ Inhalation Powder](#), and additional information at www.TYVASOHCP.com or call 1-877-UNITHER (1-877-864-8437).

United Therapeutics: Enabling Inspiration

We build on the strength of our research and development expertise and a distinctive, entrepreneurial culture that encourages diversity, innovation, creativity, sustainability, and, simply, fun. Since inception, our mission has been to find a cure for pulmonary arterial hypertension and other life-threatening diseases. Toward this goal we have successfully gained FDA approval for five medicines, we are always conducting new clinical trials, and we are working to create an unlimited supply of manufactured organs for transplantation.

We are the first publicly traded biotech or pharmaceutical company to take the form of a public benefit corporation (**PBC**). Our public benefit purpose is *to provide a brighter future for patients through (a) the development of novel pharmaceutical therapies; and (b) technologies that expand the availability of transplantable organs*. At the same time, we seek to provide our shareholders with superior financial performance and our communities with earth-sensitive energy utilization.

You can learn more about what it means to be a PBC here: unither.com/PBC.

Forward-looking Statements

Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, among others, statements relating to the timing and success of the Tyvaso DPI launch, the anticipated benefits of Tyvaso DPI for benefit patients, and our goals of furthering our public benefit purpose, providing superior financial performance for shareholders, and providing our communities with earth-sensitive energy utilization. These forward-looking statements are subject to certain risks and uncertainties, such as those described in our periodic reports filed with the Securities and Exchange Commission, that could cause actual results to differ materially from anticipated results. Consequently, such forward-looking statements are qualified by the cautionary statements, cautionary language and risk factors set forth in our periodic reports and documents filed with the Securities and Exchange Commission, including our most recent Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. We claim the protection of the safe harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. We are providing this information as of May 24, 2022, and assume no obligation to update or revise the information contained in this press release whether as a result of new information, future events or any other reason.

TYVASO is a registered trademark of United Therapeutics Corporation.

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