Treprostinil Oral Inhalation Solution and Dry Powder Inhaler (TYVASO and TYVASO DPI) Mini-Monograph November 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The objectives of this mini-monograph are to review: 1) the new DPI dosage form of treprostinil; 2) the expanded FDA indication for treprostinil inhalation (solution and DPI) for patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD).

FDA APPROVAL	**Description/MOA**	Prostacyclin analogue
	Indication(s) Under Review	▪ **New FDA indication (2022): Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.** ▪ *Of note, treprostinil inhalation is also FDA approved (2009) to treat pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Efficacy was established predominantly in patients with NYHA Functional Class III symptoms.*
	Dosage Form(s)	▪ **New dosage form (2022): Dry powder inhalation (DPI)** o 16 mcg, 32 mcg, 48 mcg, and 64 mcg strengths; single-dose, color-coded cartridges packaged in a strips of 4. Inhaler device is packaged separately, reused for 7 days, then replaced. Contains excipient fumaryl diketopiperazine (FDKP). o Dose: 1 breath per cartridge, 4 times daily, administered about 4 hrs apart o Cartridges are stored in refrigerator. Room temperature excursions are permitted but shorten shelf life. DPI should be at room temperature for 10 min prior to use. ▪ Inhalation solution o One 2.9 ml ampule of solution used each day in the Tyvaso Inhalation System, a reusable device that requires daily cleaning. o Dose: initially 3 breaths (18 mcg) per treatment session titrated to target of 9 to 12 breaths per treatment session, 4 times daily, administered about 4 hrs apart. o Ampules are stored at room temp and are packaged 4 per foil pouch. ▪ *Of note, treprostinil parenteral infusion and oral tablet are available but not part of this review.*

CLINICAL EVIDENCE	**Study/Design**	BREEZE – open label safety and tolerability study of treprostinil DPI, 3 wks + extension
	Population	N=51 PAH patients who were on a stable regimen of treprostinil inhalation solution
	Demographics/ baseline	Mean age 56 yrs; female (84%); idiopathic/familial PAH (57%); associated with collagen vascular disease (28%); respiratory comorbidities (10%); WHO functional class: II (61%), III (28%); background therapy (98%): ERA (84%), PDE-5i (80%); baseline 6MWD (419 m)
	Intervention	**Treprostinil inhalation solution QID** / **Treprostinil DPI QID** 6 to 7 breaths / 32 mcg 8 to 10 breaths / 48 mcg 11 to 12 breaths / 64 mcg
	Results	▪ **Primary endpts (reported AEs):** withdrawal due to AEs (n=2); most common AEs: cough (35%), headache (16%), dyspnea (8%); no bronchospastic events; no SAEs considered related to DPI inhaler ▪ **Select secondary/exploratory endpts:** Δ6MWD (+11.5 m), increased pt satisfaction ▪ **PK:** similar AUCs for inhaled solution vs. DPI except for higher Cmax with DPI.
	Summary	**No observed decrease in 6MWD, worsening of patient reported outcomes, or apparent increase in AEs with treprostinil DPI in patients switched from inhalation solution.**

CLINICAL EVIDENCE	**Study/Design**	INCREASE - randomized, double-blind, placebo-controlled, 16-wk trial in PH-ILD
	Population	N=326; ILD diagnosed by chest CT; Group 3 PH confirmed by RHC (PVR >3 Wood units, PCWP ≤15 mmHg, mPAP ≥25 mm Hg); 6MWD ≥100 m; stable ILD treatment permitted; excluded pts on PAH treatment in past 60 days
	Demographics/ baseline	Mean age 66 yrs; female (47%), idiopathic interstitial pneumonia (45%), combined pulmonary fibrosis and emphysema (25%); 6MWD (260m), median treprostinil dose: 12 breaths (72 mcg) 4x daily; on background ILD treatment (23%)
	Intervention	Initial dose of 3 breaths (6 mcg per breath) 4x daily; target dose of 9 breaths; max dose of 12 breaths
	Results	▪ **Primary endpt:** Δ6MWD: TRE (+21m) vs. PBO (-10m) = +31m treatment effect (p<0.001) ▪ **Select secondary/exploratory endpts:** NT-proBNP ratio to baseline TRE (0.85) vs. PBO (1.46) = 0.58 treatment effect (p<0.001); any clinical worsening TRE 23% vs. PBO 33% (p=0.04); hospitalization TRE (11%) vs. PBO (15%) (NS); patient reported QoL SGRQ (NS).
	Summary	**Treprostinil increased 6MWD vs. placebo; improvements in the composite outcome for clinical worsening driven by worsening 6MWD in placebo group**

SAFETY	**Contraindications**	None
	Boxed Warnings	None
	Warnings/ Precautions	Risk of symptomatic hypotension, bleeding (inhibits platelet aggregation), bronchospasm, drug interactions with CYP2C8 inhibitors (increased adverse effects of treprostinil) or CYP2C8 inducers (decreased effectiveness of treprostinil)
	Adverse Reaction	Cough, headache, dyspnea, dizziness, nausea, fatigue, diarrhea

Abbreviations: 6MWD=6-minute walk distance; AUC=area under the curve; AEs=adverse effects; MOA=mechanism of action; N=number of patients; NS=not statistically significant; NYHA=New York Heart Association; PBO=placebo; QID=four times daily; QoL=quality of life; SAEs=serious adverse events; sGC=soluble guanylate cyclase stimulator; SGRQ=St. George's Respiratory Questionnaire; TRE=treprostinil; WHO=World Health Organization

Conclusions/Projected Place in Therapy

- **Treprostinil inhalation (solution or DPI) for PH-ILD**
  - There is limited and conflicting evidence on the use of PAH-specific medications in patients with WHO Group 3 PH. Studies evaluating endothelin receptor antagonists (ERAs) and sildenafil (phosphodiesterase-5 inhibitor, PDE-5i) for the treatment of ILD have yielded negative results. In patients with PH associated with ILD, safety signals of worse outcomes have been identified with ambrisentan (ERA) and riociguat (soluble guanylate cyclase stimulator).
  - FDA approval of treprostinil inhalation for PH associated with ILD was based on one 16-week, placebo-controlled trial (n=326) where treprostinil inhalation was shown to improve 6MWD, NT-proBNP, and clinical worsening (driven by deteriorating 6MWD in placebo group). The most common adverse effects were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea, which are typical with prostacyclin treatment. There was no excess of cardiopulmonary-related hospitalizations or worsening of pulmonary function testing variables identified with treprostinil treatment. Long term data are lacking.
  - European Pulmonary Hypertension Guidelines (2022) provide a weak recommendation for inhaled treprostinil, stating that it may be considered in patients with PH associated with ILD.
- **Treprostinil DPI:**
  - Safety and tolerability of treprostinil DPI was evaluated in a PAH population in the open label BREEZE study (n=51 PAH) where no decline in 6MWD, worsening of patient reported outcomes, or apparent increase in adverse effects was observed in a 3-week treatment phase or the optional extension phase.
  - No additional evidence for effectiveness was submitted to the FDA for the DPI dosage form. Evidence for relative bioavailability was based on a crossover study (n=36 healthy volunteers) where similar AUCs were observed for the DPI and solution formulations, though Cmax for the DPI was greater than 120% of the solution formulation at all doses.
  - Treprostinil DPI contains the excipient FDKP. FDKP is also an excipient in the inhaled insulin product (AFREZZA), which carries a boxed warning on the risk of acute bronchospasm in patients with chronic lung disease. Per the FDA review of treprostinil DPI, no bronchospastic adverse events or safety signals were identified in the BREEZE study, which included some patients (10%) with underlying lung disease.

- Treprostinil DPI is a higher cost, new formulation available as single-use cartridges to be used in an inhaler device that is discarded every 7 days. Treprostinil DPI may be considered as an alternative to the liquid inhalation nebulized formulation in patients with PAH or PH-ILD.

References

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