

Clinical Policy: Treprostinil (Orenitram, Remodulin, Tyvaso, Tyvaso DPI)

Reference Number: CP.PHAR.199

Effective Date: 03.16

Last Review Date: 02.24

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Treprostinil (Orenitram[®], Remodulin[®], Tyvaso[®], Tyvaso DPI[™]) is a prostacyclin analog.

FDA Approved Indication(s)

Orenitram, Remodulin, Tyvaso and Tyvaso DPI are indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve exercise ability.

- Orenitram is also indicated to delay disease progression.
- Remodulin is also indicated to reduce the rate of clinical deterioration in patients with PAH requiring transition from epoprostenol (Flolan[®], Veletri[®]). The risks and benefits of each drug should be carefully considered prior to transition.
- Tyvaso and Tyvaso DPI are indicated for the treatment of 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%)

For PAH, studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH, PAH associated with congenital systemic-to-pulmonary shunts, or PAH associated with connective tissue diseases. Nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor) with study duration of 12 weeks.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation[®] that treprostinil is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria**A. Pulmonary Arterial Hypertension (must meet all):**

1. Diagnosis of PAH;
2. Prescribed by or in consultation with a cardiologist or pulmonologist;

3. Failure of a calcium channel blocker (*see Appendix B*), unless member meets one of the following (a or b):
 - a. Inadequate response or contraindication to acute vasodilator testing;
 - b. Contraindication or clinically significant adverse effects to calcium channel blockers are experienced;
4. If request is for brand Remodulin, member must use generic treprostinil, unless contraindicated or clinically significant adverse effects are experienced;
5. Request meets one of the following (a, b, c, or d):
 - a. Orenitram: If member requires titration, provider must submit a titration plan;
 - b. Remodulin: Provider must submit treatment plan detailing pump rate, dose, quantity (in mL), and frequency of cassette change;
 - c. Tyvaso: Dose does not exceed 12 breaths per treatment session (72 mcg of treprostinil) four times daily to be used with the Tyvaso Inhalation System (a second back-up system device is recommended);
 - d. Tyvaso DPI: Dose does not exceed 64 mcg per treatment session (1 cartridge) four times daily to be used with the Tyvaso DPI inhaler (256 mcg [4 cartridges] per day).

Approval duration:

Medicaid/HIM – 6 months

Commercial – 12 months or duration of request, whichever is less

B. Pulmonary Hypertension Associated with Interstitial Lung Disease (must meet all):

1. Diagnosis of PH-ILD;
2. Member has WHO Group 3 pulmonary hypertension;
3. Request is for Tyvaso or Tyvaso DPI;
4. Prescribed by or in consultation with a cardiologist or pulmonologist;
5. Age \geq 18 years;
6. Member has had right heart catheterization which confirmed all of the following (a, b, and c):
 - a. Pulmonary vascular resistance (PVR) $>$ 3 Wood Units (WU);
 - b. Pulmonary capillary wedge pressure (PCWP) of $<$ 15 mmHg;
 - c. Mean pulmonary arterial pressure (mPAP) of \geq 25 mmHg;
7. If member's pulmonary hypertension is due to connective tissue disease, member's baseline forced vital capacity (FVC) is $<$ 70%;
8. Dose does not exceed either one of the following (a or b):
 - a. Tyvaso: 12 breaths per treatment session (72 mcg of treprostinil) four times daily to be used with the Tyvaso Inhalation System (a second back-up system device is recommended);
 - b. Tyvaso DPI: 64 mcg per treatment session (1 cartridge) four times daily to be used with the Tyvaso DPI inhaler (256 mcg [4 cartridges] per day).

Approval duration:

Medicaid/HIM – 6 months

Commercial – 12 months or duration of request, whichever is less

C. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Pulmonary Arterial Hypertension (must meet all):

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
2. Member is responding positively to therapy;
3. If request is for brand Remodulin, member must use generic treprostinil, unless contraindicated or clinically significant adverse effects are experienced;
4. Request meets one of the following (a, b, c, or d):
 - a. Orenitram: If member requires titration, provider must submit a titration plan;
 - b. Remodulin: Provider must submit treatment plan detailing pump rate, dose, quantity (in mL) and frequency of cassette change;
 - c. Tyvaso: If request is for a dose increase, new dose does not exceed 12 breaths per treatment session (72 mcg of treprostinil) four times daily to be used with the Tyvaso Inhalation System (a second back-up system device is recommended);
 - d. Tyvaso DPI: If request is for a dose increase, new dose does not exceed 64 mcg per treatment session (1 cartridge) four times daily to be used with the Tyvaso DPI inhaler (256 mcg [4 cartridges] per day).

Approval duration:

Medicaid/HIM – 12 months

Commercial – 12 months or duration of request, whichever is less

B. Pulmonary Hypertension Associated with Interstitial Lung Disease (must meet all):

1. Member meets one of the following (a or b):

- a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);
2. Request is for Tyvaso or Tyvaso DPI;
 3. Member is responding positively to therapy;
 4. If request is for a dose increase, new dose does not exceed either one of the following (a or b):
 - a. Tyvaso: 12 breaths per treatment session (72 mcg of treprostinil) four times daily to be used with the Tyvaso Inhalation System (a second back-up system device is recommended);
 - b. Tyvaso DPI: 64 mcg per treatment session (1 cartridge) four times daily to be used with the Tyvaso DPI inhaler (256 mcg [4 cartridges] per day).

Approval duration:

Medicaid/HIM – 12 months

Commercial – 12 months or duration of request, whichever is less

C. Other diagnoses/indications (must meet 1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
 - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
 - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CTEPH: chronic thromboembolic
pulmonary hypertension

FC: functional class

FDA: Food and Drug Administration

FVC: forced vital capacity
 mPAP: mean pulmonary arterial pressure
 NYHA: New York Heart Association
 PA: physical ability
 PAH: pulmonary arterial hypertension

PCWP: pulmonary capillary wedge pressure
 PH: pulmonary hypertension
 PVR: pulmonary vascular resistance
 WHO: World Health Organization
 WU: Wood Units

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
nifedipine (Adalat [®] CC, Procardia XL [®])	60 mg PO QD; may increase to 120 to 240 mg/day	240 mg/day
diltiazem (Dilacor XR [®] , Dilt-XR [®] , Cardizem [®] CD, Cartia XT [®] , Tiazac [®] , Taztia XT [®] , Cardizem [®] LA, Matzim [®] LA)	720 to 960 mg PO QD	960 mg/day
amlodipine (Norvasc [®])	20 to 30 mg PO QD	30 mg/day

Therapeutic alternatives are listed as Brand name[®] (generic) when the drug is available by brand name only and generic (Brand name[®]) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
 - Orenitram: Severe hepatic impairment (Child Pugh Class C)
- Boxed warnings(s): none reported

Appendix D: Pulmonary Hypertension: WHO Classification

- Group 1: PAH
- Group 2: PH due to left heart disease
- Group 3: PH due to lung disease and/or hypoxemia
- Group 4: CTEPH
- Group 5: PH due to unclear multifactorial mechanisms

Appendix E: Pulmonary Hypertension: WHO/NYHA Functional Classes (FC)

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
Monitoring for progression of PH and treatment of co-existing conditions	I	Comfortable at rest	No limitation	Ordinary PA does not cause undue dyspnea or fatigue, chest pain, or near syncope.	

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
Advanced treatment of PH with PH-targeted therapy – see Appendix F**	II	Comfortable at rest	Slight limitation	Ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.	
	III	Comfortable at rest	Marked limitation	Less than ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.	
	IV	Dyspnea or fatigue may be present at rest	Inability to carry out any PA without symptoms	Discomfort is increased by any PA.	Signs of right heart failure

*PH supportive measures may include diuretics, oxygen therapy, anticoagulation, digoxin, exercise, pneumococcal vaccination. **Advanced treatment options also include calcium channel blockers.

Appendix F: Pulmonary Hypertension: Targeted Therapies

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
Reduction of pulmonary arterial pressure through vasodilation	Prostacyclin* pathway agonist <i>*Member of the prostanoid class of fatty acid derivatives.</i>	Prostacyclin	Epoprostenol	Velettri (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV) Tyvaso, Tyvaso DPI (inhalation)
			Iloprost	Ventavis (inhalation)
		Non-prostanoid prostacyclin receptor (IP receptor) agonist	Selexipag	Uptravi (oral tablet)
	Endothelin receptor antagonist (ETRA)	Selective receptor antagonist	Ambrisentan	Letairis (oral tablet)
		Nonselective dual action receptor antagonist	Bosentan	Tracleer (oral tablet)
			Macitentan	Opsumit (oral tablet)
	Nitric oxide-cyclic guanosine	Phosphodiesterase type 5 (PDE5) inhibitor	Sildenafil	Revatio (IV, oral tablet, oral suspension)

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
	monophosphate enhancer		Tadalafil	Adcirca (oral tablet)
		Guanylate cyclase stimulant (sGC)	Riociguat	Adempas (oral tablet)

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Treprostinil (Orenitram)	0.25 mg PO BID or 0.125 mg PO TID; can be increased every 3-4 days as tolerated	Based on tolerability
Treprostinil (Remodulin)	1.25 ng/kg/min SC or IV; can be increased weekly based on clinical response	Based on weight and tolerability
Treprostinil (Tyvaso)	4 treatment sessions per day with 3 breaths (18 mcg) per treatment session, titrated up to 12 breaths (72 mcg) per treatment session	72 mcg per treatment session (288 mcg/day)
Treprostinil (Tyvaso DPI)	4 treatment sessions per day approximately 4 hours apart, during waking hours. Initial dosage: one 16 mcg cartridge per treatment sessions. Dosage should be increased by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals, if tolerated. Titrate to a target maintenance dose of 48 mcg to 64 mcg per treatment, 4 times daily	64 mcg per treatment session (256 mcg/day)

VI. Product Availability

Drug	Availability
Treprostinil (Orenitram)	Extended-release tablets: 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, 5 mg
Treprostinil (Remodulin)	20 mL vials: 20 mg, 50 mg, 100 mg, 200 mg
Treprostinil (Tyvaso)	Solution for inhalation (ampule): 1.74 mg/2.9 mL
Treprostinil (Tyvaso DPI)	Inhalation powder: single-dose plastic cartridges containing 16, 32, 48, or 64 mcg of treprostinil as a dry powder formulation

VII. References

1. Orenitram Prescribing Information. Research Triangle, NC: United Therapeutics Corp.; August 2023. Available at: <https://www.orenitramhcp.com/media/content/files/Orenitram-Prescribing-Information.pdf>. Accessed October 3, 2023.
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12. Generic Treprostinil Injection Launched for Intravenous Use. Pulmonary Hypertension Association. April 2019. Available at: <https://phassociation.org/>. Accessed August 6, 2020.
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15. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*, Volume 43, Issue 38, 7 October 2022, Pages 3618–3731, <https://doi.org/10.1093/eurheartj/ehac237>.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3285	Injection, treprostinil, 1mg
J7686	Treprostinil, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, 1.74 mg

HCPCS Codes	Description
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified (including Orenitram and Tyvaso DPI)

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2020 annual review: no significant changes; added statement that titration plan be submitted for Orenitram and treatment plan detailing dose, quantity, and frequency be submitted for Remodulin; removed HIM NF disclaimer statements; references reviewed and updated.	11.26.19	02.20
Added preferencing for generic Remodulin prior to allowing Remodulin brand for all indications.	02.27.20	
Added lack of pump access for subcutaneous infusion as an example of medical justification supporting inability to use generic Remodulin.	05.20.20	
Revised the example of medical justification supporting inability to use generic Remodulin from “lack of subcutaneous infusion pump access” to “IV administration not suitable and subcutaneous generic Remodulin is not available”; added generic redirection to Section II; added Appendix G; references updated.	08.06.20	
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; Added coding implications for J7686; references reviewed and updated.	10.12.20	02.21
RT4: added criteria for new indication for PH-ILD; updated max recommended dose for PAH per PI.	05.13.21	08.21
Removed “or IV administration is not suitable and subcutaneous generic Remodulin is not available” as a potential exception for generic redirection requirement, as generic SC treprostinil is now available.	09.10.21	
1Q 2022 annual review: no significant changes; references reviewed and updated.	11.09.21	02.22
RT4: added new dosage form, Tyvaso DPI.	06.13.22	
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less. Template changes applied to other diagnoses/indications and continued therapy section.	06.23.22	11.22
1Q 2023 annual review: added Tyvaso DPI dosage form to criteria; references reviewed and updated.	11.18.22	02.23
1Q 2024 annual review: no significant changes; revised language in FDA approved indication(s) to align with PI; removed commercially unavailable branded products from Appendix B; clarified HCPC	10.03.23	02.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
code [J8499] is also applicable to Tyvaso DPI; removed inactive HCPC code [J7699]; references reviewed and updated.		

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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