Clinical Policy: Treprostinil (Orenitram, Remodulin, Tyvaso)

Reference Number: AZ.CP.PHAR.199
Effective Date: 9.25.19
Last Review Date: 08.21
Line of Business: Arizona Medicaid (AzCH-CCP and Care1st) Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Treprostinil (Orenitram®, Remodulin®, Tyvaso®) is a prostacyclin analog.

FDA Approved Indication(s)

Orenitram, Remodulin, and Tyvaso 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 Flolan® (epoprostenol sodium). The risks and benefits of each drug should be carefully considered prior to transition.

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. When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

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 Arizona Complete Health-Complete Care Plan and Care1st that Orenitram, Remodulin, and Tyvaso are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Pulmonary Arterial Hypertension (must meet all):

1. Diagnosis of PAH;
2. Documentation of NYHA functional class II, III, or IV:
   a. If class II, failure of a trial of one PDE-5 inhibitor (tadalafil, sildenafil) and one ETRA (bosentan, ambrisentan) for at least 30 days, unless contraindicated or clinically significant adverse effects are experienced;
3. Prescribed by or in consultation with a cardiologist or pulmonologist;
4. Right heart catheterization (RHC) results with a mean pulmonary arterial pressure (PAP) $\geq$ 25 mm Hg;

5. 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;
6. If Remodulin is requested, must meet both of the following (a and b):
   a. Medical justification supports inability to use the generic treprostinil (e.g., contraindications to excipients in the authorized generic or lack of pump access for subcutaneous infusion);
   b. All of the following is included on the request (i-v):
      i. Titration plan with current and goal doses;
      ii. Pump rate;
      iii. Volume injected in cassette;
      iv. Frequency of cassette change;
      v. Dosing weight;
7. If Orenitram is requested, must include all of the following (a, b, and c):
   a. Titration plan with current and goal doses;
   b. All tablet strengths needed for titration;
   c. Number of tablets of each strength used to achieve dosing;
8. If Tyvaso is requested, 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).

Approval duration: 6 months

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;
4. Prescribed by or consultation with a cardiologist or pulmonologist;
5. Age ≥ 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 ≥ 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 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).

Approval Duration: 6 months

C. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona Medicaid.

II. Continued Therapy

A. Pulmonary Arterial Hypertension (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy;
3. If Remodulin is requested, must meet both of the following (a and b):
   a. Medical justification supports inability to use the generic Remodulin (e.g., contraindications to excipients in the authorized generic or lack of pump access for subcutaneous infusion);
   b. All of the following is included on the request (i-v):
      i. Titration plan with current and goal doses;
      ii. Pump rate;
      iii. Volume injected in cassette;
      iv. Frequency of cassette change;
      v. Dosing weight;
4. If Orenitram is requested, must include all of the following (a, b, and c):
   a. Titration plan with current and goal doses;
   b. All tablet strengths needed for titration;
   c. Number of tablets of each strength used to achieve dosing;
5. If Tyvaso is requested and 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).

Approval duration: 12 months

B. Pulmonary Hypertension Associated with Interstitial Lung Disease (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Request is for Tyvaso;
3. Member is responding positively to therapy;
4. 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).

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

Approval duration: Duration of request or 12 months (whichever is less); or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): AZ.CP.PMN.53 for Arizona 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 – AZ. CP.PMN.53 for Arizona Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ETRA: endothelin receptor antagonist
FDA: Food and Drug Administration
FC: functional class
NYHA: New York Heart Association
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
PDE-5: phosphodiesterase type 5
WHO: World Health Organization

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, Afeditab® CR, Procardia®, 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 (pulmonary arterial hypertension)
- Group 2: PH due to left heart disease

- Group 3: PH due to lung disease and/or hypoxemia
- Group 4: CTEPH (chronic thromboembolic pulmonary hypertension)
- 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.	
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	Prostacyclin* pathway agonist **Member of the prostanoid class of fatty acid derivatives.*	Prostacyclin	Epoprostenol	Veletri (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV) Tyvaso (inhalation)
			Iloprost	Ventavis (inhalation)
		Non-prostanoid prostacyclin receptor (IP receptor) agonist	Selexipag	Uptravi (oral tablet)

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
arterial pressure through vasodilation	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 monophosphate enhancer	Phosphodiesterase type 5 (PDE5) inhibitor	Sildenafil	Revatio (IV, oral tablet, oral suspension)
			Tadalafil	Adcirca (oral tablet)
		Guanylate cyclase stimulant (sGC)	Riociguat	Adempas (oral tablet)

Appendix G: General Information

- Generic treprostinil injection is approved by the U.S. Food and Drug Administration for both intravenous and subcutaneous use. However, generic treprostinil for subcutaneous use has limited availability of CADD-MS® 3 pump and subcutaneous pump supplies. Patients prescribed generic treprostinil will only be able to use the medication intravenously until an alternative supplier for generic treprostinil subcutaneous delivery devices is identified.
- Patients prescribed branded Remodulin may continue to use the medication both intravenously and subcutaneously, if they have access to the subcutaneous supplies.

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	288 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

VII. References

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13. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *NEJM.* 2021;384:325-34.

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

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	09.25.19	10.19
Q1 2020 annual review; no significant changes	01.13.2020	01.2020
Updated language that brand Remodulin may be used if medical justification is provided that member has contraindications to excipients in generic formulation or lack of pump access for subcutaneous infusion	06.19.20	07.20
Q1 2021 review: added Appendix G- General Information; no significant changes; references reviewed and updated.	01.21	02.12.21
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21
Q3 2021 review: added criteria for new indication PH-ILD; updated max recommended dose for Tyvaso per PI; references reviewed and updated.	07.22.21	07.21

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.