Clinical Policy: Treprostinil (Orenitram, Remodulin, Tyvaso)

Reference Number: PA.CP.PHAR.199
Effective Date: 01/18
Last Review Date: 01/19

Coding Implications
Revision Log

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. 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
It is the policy of health plans affiliated with Pennsylvania Health and Wellness that Orenitram, Remodulin, 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. 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, b or c):
   a. Inadequate response or contraindication to acute vasodilator testing;
   b. Contraindication or clinically significant adverse effects to calcium channel blockers are experienced;
   c. Members already taking and stabilized on treprostinil will not be required to change therapy;
4. If Tyvaso is requested, dose does not exceed 9 breaths per treatment session (54 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. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. Pulmonary Arterial Hypertension (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. If Tyvaso is requested and request is for a dose increase, dose does not exceed 9 breaths per treatment session (54 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. Other diagnoses/indications (must meet 1 or 2)**:**

Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; **Approval duration: Duration of request or 12 months (whichever is less)**; or

1. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:
Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, inhibition of platelet aggregation, and inhibition of smooth muscle cell proliferation.

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FC: functional class
FDA: Food and Drug Administration
NYHA: New York Heart Association
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
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	Prostacyclin* pathway agonist	Prostacyclin	Epoprostenol	Veletri (IV) Flolan (IV)

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
pulmonary arterial pressure through vasodilation	**Member of the prostanoid class of fatty acid derivatives.*			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)
	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)

IV. 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 9 breaths (54 mcg) per treatment session	216 mcg/day

V. 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

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	Approval Date
Removed WHO/NYHA classifications from initial criteria since specialist is involved in care. References reviewed and updated.	02/18	
1Q 2019 annual review: references reviewed and updated.	01/19	

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