Clinical Policy: Treprostinil (Orenitram, Remodulin, Tyvaso)

Reference Number: ERX.SPA.36
Effective Date: 07.01.16
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

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.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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. 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, medical justification supports inability to use generic treprostinil (e.g., contraindications to excipients in the generic formulation, or IV administration is not suitable and subcutaneous generic Remodulin is not available) (*see Appendix G);*
5. Request meets one of the following (a, b, or c):
   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 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

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for brand Remodulin, medical justification supports inability to use generic treprostinil (e.g., contraindications to excipients in the generic formulation, or IV administration is not suitable and subcutaneous generic Remodulin is not available) (*see Appendix G);*
4. Request meets one of the following (a, b, or c):
   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 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)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

IV. 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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): severe hepatic impairment (Child Pugh Class C) [*Orenitram only*]
- 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 D: 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, and 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	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
pressure through vasodilation	Endothelin receptor antagonist	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 (PDE-5) inhibitor	Sildenafil	Revatio (IV, oral tablet, oral suspension)
			Tadalafil	Adcirca (oral tablet)
		Guanylate cyclase stimulant	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 9 breaths (54 mcg) per treatment session	216 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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Reviews, Revisions, and Approvals	Date	P&T Approval Date
FC II is added to the prostanoid class of PH drugs. An efficacy statement is added to the continuation criteria. Initial and continuation durations increased to 6 and 12 months respectively. Appendices covering PH groups, functional class and therapies reorganized.	04.17	05.17
1Q18 annual review: Converted to new template. Removed WHO/NYHA classification from initial criteria. References reviewed and updated.	11.20.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	11.20.18	02.19
1Q 2020 annual review: no significant changes; added statement requiring titration plan be submitted for Orenitram and treatment plan detailing dose, quantity, and frequency be submitted for Remodulin; 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 reviewed and updated.	10.12.20	02.21

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.