Clinical Policy Title:	treprostinil
Policy Number:	RxA.258
Drug(s) Applied:	Orenitram®, Remodulin®, Tyvaso®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Treprostinil is a prostacyclin analog.

Injectable treprostinil is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 in patients with New York Heart Association (NYHA) Class II to IV symptoms to decrease exercise-associated symptoms. Remodulin® is also indicated to reduce the rate of clinical deterioration in patients with PAH requiring transition from epoprostenol.
Treprostinil inhalation solution is indicated for treatment of PAH (WHO Group 1) in patients with NYHA Class III symptoms to improve exercise ability. It is also indicated for treatment if PAH associated with interstitial lung disease (WHO Group 3) to improve exercise ability.
Oral Treprostinil is indicated for treatment of PAH (WHO Group 1) in patients with WHO Functional Class II to III symptoms to delay disease progression and to delay disease progression and to improve exercise capacity or PAH associated with connective tissue disease.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
treprostinil (Orenitram®)	Pulmonary arterial hypertension	0.125 mg orally thrice a day or 0.25 mg orally twice a day; can be increased every 3-4 days as tolerated*	Based on Tolerability
treprostinil (Remodulin®)		1.25 ng/kg/min subcutaneous or intravenous; can be increased weekly based on clinical response and target dose is generally 40 to 80ng/kg/minute but can he higher.	Based on weight and tolerability

treprostinil (Tyvaso®)		18 mcg (3 inhalations) 4 times a day administered ever 4 hours while patient is awake; if 3 inhalations are not tolerated, reduce to 1-2 inhalations, then increase to 3 as tolerated.	216 mcg/day

* If transitioning from intravenous (IV) to subcutaneous (SC) Remodulin ® the Orenitram® dose should be increased while simultaneously decreasing the IV/SC infusion rate.

Dosage Forms

- 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.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Pulmonary Arterial Hypertension (must meet all):

1. Diagnosis of WHO Group 1 pulmonary arterial hypertension;
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 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
Commercial: 12 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Pulmonary Arterial Hypertension (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or member has previously met initial approval criteria;
2. Member is responding positively to therapy (i.e. disease stability or improvement);
3. If Tyvaso® is requested and request is for a dose increase, new 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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
nifedipine (Procardia®, Procardia XL®)	60 mg orally once a day; may increase to 120 to 240 mg/day	240 mg/day
diltiazem (Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA)	720 to 960 mg orally once a day	960 mg/day
amlodipine (Norvasc®)	20 to 30 mg orally once a day	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 Warning(s):
  - None reported.

APPENDIX D: General Information
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):

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

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

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 **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)
	Endothelin receptor antagonist (ETRA)	Selective receptor antagonist	ambrisentan	Letairis® (oral tablet)
		Nonselective dual action receptor antagonist	bosentan	Tracleer® (oral tablet)
			macitentan	Opsumit® (oral tablet)

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
	Nitric oxidecyclic 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)

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy updated. 1. Formatting updated. 2. Criteria for approval and continued approval updated. 3. Approval duration updated. 4. Reference Updated	07/21/2020	9/14/2020
Policy updated. 1. Policy title was updated. 2. Clinical policy verbiage has been updated as 'The provision of prescriber samples…. 3. Continued therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance.." 4. APPENDIX B: Therapeutic Alternatives were updated. 5. References were reviewed and updated.	04/06/2021	06/10/2021