Clinical Policy Title:	epoprostenol
Policy Number:	RxA.302
Drug(s) Applied:	Flolan®, Veletri®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Epoprostenol (Flolan®, Veletri®) is a prostacyclin vasodilator. Flolan® and Veletri® are indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve exercise capacity.

Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
epoprostenol (Flolan®)	PAH	2 ng/kg/min IV, increased by 1-2 ng/kg/min at intervals of at least 15 minutes	Based on clinical response
epoprostenol (Veletri®)	PAH	2 ng/kg/min IV, increased by 2 ng/kg/min every 15 minutes or longer	Based on clinical response

Dosage Forms

- epoprostenol (Flolan®): Vial with powder for reconstitution: 0.5 mg, 1.5 mg
- epoprostenol (Veletri®): Vial with powder for reconstitution: 0.5 mg, 1.5 mg

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 administer 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 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 Flolan® or Veletri® is requested, member has failed or has an intolerance/contraindication to generic epoprostenol sodium.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Pulmonary Arterial Hypertension (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy.

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 (Adalat® CC, Procardia®, Procardia XL®)	60 mg PO once daily; 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 PO once daily	960 mg/day
amlodipine (Norvasc®)	20 to 30 mg PO once daily	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):
  - Congestive heart failure due to severe left ventricular systolic dysfunction

- Hypersensitivity to the drug or to structurally related compounds
- Pulmonary edema

- Boxed Warning(s):
  - None.

APPENDIX D: General Information

The most recent World Health Organization (WHO) classification has categorized PH in to five different groups based on the underlying mechanism.

- 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 coexisting 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:

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) epoprostenol (IV)
		Synthetic prostacyclin analog	treprostinil	Orenitram® (oral tablet) Remodulin® (IV) Tyvaso® (inhalation) treprostinil (IV)
			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) ambrisentan (oral tablet)
		Nonselective dual action receptor antagonist	bosentan	Tracleer® (oral tablet) bosentan (oral tablet)
			macitentan	Opsumit® (oral tablet)
	Nitric oxidecyclic guanosine monophosphate enhancer	Phosphodiesterase type 5 (PDE5) inhibitor	sildenafil	Revatio® (IV, oral tablet, oral suspension) sildenafil (IV, oral tablet, oral suspension)
			tadalafil	Adcirca® (oral tablet) tadalafil (oral tablet)
		Guanylate cyclase stimulant (sGC)	riociguat	Adempas® (oral tablet)

References

1. Epoprostenol Sodium Prescribing Information. North Wales, PA: Teva Parenteral Medicines, Inc.; January 2021. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=56733651-d331-4e69-a6a3303756ccc53c. Accessed May 11, 2021.
2. Flolan® Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline; November 2019. Available at: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Flolan/pdf/FLOLAN-PI-PIL.PDF . Accessed May 11, 2021.
3. Veletri® Prescribing Information. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; December 2018.

Available at: https://www.veletri.com. Accessed May 11, 2021.
4. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association - developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009; 53(17): 1573-1619. Accessed May 11, 2021.
5. Taichman D, Ornelas J, Chung L, et. al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest. 2014; 146 (2): 449-475. Accessed May 11, 2021.
6. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015 Nov 24; 132(21): 2037-99. Accessed May 11, 2021.
7. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2013; 62(25 Suppl): D92-99. Accessed May 11, 2021.
8. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Kardiol Pol. 2015;73(12):1127-206. Accessed May 11, 2021.
9. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2021. Accessed with subscription at: http://www.clinicalkey.com. Accessed May 11, 2021.
10. Epoprostenol Sodium, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed May 11, 2021.
11. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report. Chest. 2019 Mar;155(3):565-586. doi: 10.1016/j.chest.2018.11.030. Epub 2019 Jan 17. Erratum in: Chest. 2021 Jan;159(1):457. PMID: 30660783.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated: Clinical Policy Title was updated to "epoprostenol"; Drug(s) Applied was updated to "Flolan®, Veletri®"; Line of Business Policy Applies to was updated to "All". 2. Clinical policy was updated: Approval duration was updated for both Initial and Continued Approval Criteria; Continued Approval was rephrased to "Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy". 3. Appendix B was updated: Discontinued brands Afeditab CR and Dilacor XR were removed. 4. References were updated.	07/28/2020	09/14/2020

Policy was reviewed: 1. Policy title table updated. 2. Clinical policy section standard verbiage was updated to include "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 for therapeutic alternatives standard verbiage was updated to "Below are suggested therapeutic alternatives based on clinical guidance...". 5. Appendix C for contraindications updated to include pulmonary edema. 6. References were updated.	05/11/2021	06/10/2021