Clinical Policy: Epoprostenol Sodium (Flolan, Veletri)

Reference Number: PA.CP.PHAR.192
Effective Date: 01/2018
Last Review Date: 01/2025

Description
Epoprostenol (Flolan®, Veletri®) is a prostacyclin.

FDA Approved Indication(s)
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.

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 of PA Health & Wellness that epoprostenol, Flolan and Veletri is **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 a calcium channel blocker are experienced;
   c. Members already taking and stabilized on epoprostenol sodium will not be required to change therapy;
4. If request is for brand Flolan or brand Veletri, member must use generic epoprostenol sodium, unless contraindicated or clinically significant adverse effects are experienced.

Approval duration: 6 months

B. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

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

1. Currently receiving medication via PA Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy.

3. If request is for brand Flolan or brand Veletri, member must use generic epoprostenol sodium, unless contraindicated or clinically significant adverse effects are experienced.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.PHARM.01) applies;
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to PA.CP.PMN.53

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 – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CTEPH: chronic thromboembolic pulmonary hypertension
FC: functional class
FDA: Food and Drug Administration
NYHA: New York Heart Association
PA: physical activity
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, Procardia XL®)†	30 mg PO QD; may increase to 60 to 120 mg BID	240 mg/day
diltiazem (Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Cardizem® LA, Matzim® LA)	60 mg PO QD; may increase to 120 to 360 mg BID	720 mg/day
amlodipine (Norvasc®)†	5 mg PO QD; may increase to 15 to 30 mg/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.
†Off-label

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Congestive heart failure due to severe left ventricular systolic dysfunction

- Pulmonary edema (Veletri only)
- Hypersensitivity to the drug or to structurally related compounds

- Boxed Warning(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 arterial pressure	Prostacyclin* pathway agonist **Member of the prostanoid class*	Prostacyclin	Epoprostenol	Veletri (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV)

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
through vasodilation	*of fatty acid derivatives.*			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)

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Epoprostenol (Flolan)	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)	2 ng/kg/min IV, increased by 2 ng/kg/min every 15 minutes or longer	Based on clinical response

VI. Product Availability

Drug Name	Availability
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

VII. References

1. Epoprostenol Sodium Prescribing Information. Billerica, MA: Sun Pharmaceuticals Industries, Inc; October 2024. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=db57e498-db20-45e8-8298-b0cf0811d270. Accessed November 7, 2024.
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3. Veletri Prescribing Information. Titusville, NJ: Actelion Pharmaceuticals US, Inc.; July 2022. Available at: www.veletri.com. Accessed November 7, 2024.
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12. Yaghi S, Novikov A, Trandafirescu T. Clinical update on pulmonary hypertension. *J Investig Med*. 2020; 0:1-7. doi:10.1136/jim-2020-001291.
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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
J1325	Injection, epoprostenol, 0.5 mg

Reviews, Revisions, and Approvals	Date
Removed WHO/NYHA classifications from initial criteria since specialist is involved in care. References reviewed and updated.	02/2018
1Q 2019 annual review: references reviewed and updated.	01/2019
Q1 2020: policy retired	01/2020

Reviews, Revisions, and Approvals	Date
1Q 2021 annual review: reintroduced policy; no significant changes; references reviewed and updated.	01/2021
1Q 2022 annual review: revised medical justification language to "must use" language for generic redirection and treatment plan; references reviewed and updated.	01/2022
1Q 2023 annual review: no significant changes; references reviewed and updated.	01/2023
1Q 2024 annual review: no significant changes; removed commercially unavailable branded products from Appendix B; clarified Veletri product availability description to describe a "powder for reconstitution" per PI; references reviewed and updated.	01/2024
1Q 2025 annual review: in Policy/Criteria, clarified criteria also applies to brand Flolan and Veletri; in Appendix B per Clinical Pharmacology, removed commercially unavailable branded products, updated dosing regimens; clarified drugs used for off-label indications; references reviewed and updated.	01/2025