Clinical Policy: Epoprostenol Sodium (Flolan, Veletri)
Reference Number: ERX.SPMN.86
Effective Date: 07/16
Last Review Date: 06/16

See Important Reminder at the end of this policy for important regulatory and legal information.

Policy/Criteria
It is the policy of health plans affiliated with Envolve Pharmacy Solutions® that epoprostenol (generic epoprostenol sodium, Flolan®, and Veletri®) is medically necessary when the following criteria are met:

I. Initial Approval Criteria
A. Pulmonary Arterial Hypertension (PAH) (must meet all):
   1. Prescribed by or in consultation with a cardiologist or pulmonologist experienced in the diagnosis and treatment of pulmonary hypertension;
   2. Diagnosis of PAH World Health Organization (WHO) Group 1 (appendix B) confirmed by right heart catheterization and with one of the following:
      a. Inadequate response or contraindication to acute vasodilator testing; or
      b. Trial and failure of, or contraindication to, calcium channel blockers;
   3. WHO/New York Heart Association (NYHA) functional class III or IV (appendix C);
   4. If Flolan or Veletri are requested, member has failed or has an intolerance/contraindication to generic epoprostenol sodium.

   Approval Duration: 3 months

B. Other diagnoses/indications: Refer to ERX.SPMN.16 - Global Biopharm Policy.

II. Continued Approval
A. Pulmonary Arterial Hypertension (PAH) (must meet all):
   1. Currently receiving medication via health plan benefit or member has previously met all initial approval criteria.

   Approval Duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy;
   2. Refer to ERX.SPMN.16 - Global Biopharm Policy.
Background

Description/Mechanism of Action:
Epoprostenol (PGI, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation. Epoprostenol has 2 major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation.

- Epoprostenol sodium for injection (generic) is sterile sodium salt formulated for intravenous (IV) administration. Each vial of epoprostenol sodium for injection contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 3.76 mg glycine, 2.93 mg sodium chloride, and 50 mg mannitol. Sodium hydroxide may have been added to adjust pH.
- Flolan (epoprostenol sodium) for injection is sterile sodium salt that is a white or off-white powder formulated for IV administration. Each vial of FLOLAN contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 3.76 mg glycine, 50 mg mannitol, and 2.93 mg sodium chloride. Sodium hydroxide may have been added to adjust pH.
- Veletri (epoprostenol sodium) is the sodium salt of epoprostenol, formulated as a sterile lyophilized powder for IV administration. Each vial of VELETRI contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 100 mg sucrose, and 50 mg arginine. Sodium hydroxide is added to adjust pH.

FDA Approved Indications:
Epoprostenol sodium (generic) is a prostacyclin vasodilator/IV injectable indicated for:
- Treatment of PAH (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA FC III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Flolan (epoprostenol sodium) is a prostacyclin vasodilator/IV injectable indicated for:
- Treatment of PAH (WHO Group I) to improve exercise capacity. Trials establishing effectiveness included predominantly (97%) patients with New York Heart Association (NYHA) FC III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).

Veletri is (epoprostenol sodium) is a prostacyclin vasodilator/IV injectable indicated for:
- Treatment of PAH (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA FC III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
Appendices

Appendix A: Abbreviation Key

- CCB: calcium channel blocker
- CTEPH: chronic thromboembolic pulmonary hypertension
- ETRA: endothelin receptor antagonist
- FC: functional classification
- IP receptor agonist: prostacyclin receptor agonist
- NYHA: New York Heart Association
- PAH: pulmonary arterial hypertension
- PDE5 inhibitor: phosphodiesterase-5 inhibitor
- PH: pulmonary hypertension
- PVOD: pulmonary veno-occlusive disease
- sGC stimulator: soluble guanylate cyclase stimulator
- WHO: World Health Organization

Appendix B: WHO Classification of Pulmonary Hypertension (PH)

- Group 1 PAH (pulmonary arterial hypertension)
- Group 2 PH (left heart disease)
- Group 3 PH (lung disease)
- Group 4 PH (chronic thromboembolic pulmonary hypertension - CTEPH)
- Group 5 PH (multifactorial)

Appendix C: Advanced Therapies† for PAH WHO Group 1 in Adults by WHO/NYHA Functional Classification:

- FC I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
  - No advanced therapy indicated.
- FC II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
  - Indicated advanced therapies: ETRAs, PDE5 inhibitors, and/or sGC stimulators*.
- FC III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
  - Indicated advanced therapies: as in FC II with the addition of a parenteral or inhaled prostanoid if presence of progression and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents.
- FC IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.
  - Indicated advanced therapies: prostanoids, ETRAs, PDE5 inhibitors, and/or sGC stimulators*.

*Combinations to avoid: PDE5 inhibitors with sGC stimulators due to hypotension
† Advanced Therapies
- Prostanoids: epoprostenol* (generic*, Flolan*, Veletri*); treprostinil (Orenitram**, Remodulin*, Tyvasco+); iloprost (Ventavis+)
- PDE5 inhibitors: sildenafil (Revatio**); tadalafil (Adcirca**)
- ETRAs: ambrisentan (Letairis**); bosentan (Tracleer**); macitentan (Opsumit**)
- sGC stimulators: riociguat (Adempas**)
- IP receptor agonists: selexipag (Uptravi**)

Formulations: *injection; **oral tablet; +inhalation solution

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.

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References
1. Epoprostenol Sodium Prescribing Information. Sellersville, PA: Teva Pharmaceuticals USA; December 2012.
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.

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