VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: epoprostenol injection
- Flolan® (epoprostenol injection – GlaxoSmithKline, generic)
- Veletri® (epoprostenol injection – Actelion)

TAC APPROVAL DATE: 08/05/2015; selected revision 09/09/2015

LAY CRITERIA EFFECTIVE DATE: 10/01/2015

OVERVIEW

Epoprostenol injection is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to improve exercise capacity.[1-3] Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases. It is administered as a continuous intravenous infusion via a central venous catheter. Temporary peripheral intravenous infusion may be utilized until central access is established. Several studies have noted beneficial effects with epoprostenol therapy.[1-8]

Pulmonary hypertension can be classified into five different groups.[4] Epoprostenol is indicated in Group 1 PAH.[1-3] The five major categories of pulmonary hypertension are cited in Table 1.[17]

Table 1. Updated Classification of Pulmonary Hypertension.[17]

Group 1: Pulmonary Arterial Hypertension
Idiopathic
Heritable
BMPR2
ALK-1, ENG, SMAD9, CAV1, KCNK3
Unknown
Drug and toxin-induced
Associated with
Connective tissue disease
Human immunodeficiency virus infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Group 2: Pulmonary Hypertension Due to Left Heart Disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group 3: Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases
Group 4: Chronic Thromboembolic Pulmonary Hypertension

Table 1 (continued). Updated Classification of Pulmonary Hypertension.[17]

Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms
Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension.

BMPR2 – Bone morphogenic protein receptor type 2; ALK-1 – Activin-like receptor kinase-1; ENG – Endoglin; SMAD9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.

The WHO classification of functional status, which is an adaptation of the NYHA system, is in Table 2.[5] This provides a qualitative assessment of activity tolerance and is useful in monitoring disease progression and response to therapy.[5]

Table 2. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.[5]

Class	Description
I	Patients in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

WHO – World Health Organization.

Clinical Efficacy

The positive impact of epoprostenol injection on survival in idiopathic PAH has been demonstrated in both randomized and observational trials. Long-term epoprostenol injection therapy improves hemodynamics and quality of life in those with PAH and congenital heart disease who fail conventional therapy; improvement has also been demonstrated in those with pulmonary hypertension associated with scleroderma spectrum of disease (SSD).[6-8] Long-term epoprostenol injection therapy is the preferred treatment option for critically-ill patients with PAH.[1,4]

Chronic continuous infusion of epoprostenol injection plus conventional therapy was compared with conventional therapy alone in patients with idiopathic or heritable PAH in two prospective, open, randomized clinical trials of 8- and 12-weeks duration.[1,6] Conventional therapy included: anticoagulants (almost all patients); oral vasodilators, diuretics, and digoxin (one-half to two-thirds of patients); and supplemental oxygen (about one-half of all patients). Most patients were NYHA Functional Class III or IV (only two patients were in NYHA Functional Class II). Increases in cardiac index, stroke volume (SV) and arterial oxygen saturation and decreases in mean pulmonary artery pressure (mPAP), mean right atrial pressure (mRAP), total pulmonary resistance (TPR), and systemic vascular resistance (SVR) were observed in patients who received epoprostenol injection chronically compared with those who did not. In an open, non-randomized study, these hemodynamic improvements appeared to persist when epoprostenol injection was administered for 36 months.[1] Statistically significant improvements were observed in exercise capacity, as measured by 6-minute walk distance, in those given continuous intravenous epoprostenol injection plus conventional therapy (n = 52) for 8 or 12 weeks compared with those receiving conventional therapy alone (n = 54). Improvements were noted as soon as the first week of therapy and increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue. Survival was improved in NYHA Functional Class III and Class IV primary pulmonary hypertension patients treated with epoprostenol injection for 12 weeks in an open, randomized, parallel study.[1] At the end of the treatment period 20% of patients (n = 8/40) receiving conventional therapy alone died, while none of the 41 patients receiving epoprostenol injection therapy died (P = 0.003).

Epoprostenol injection has also proven efficacious for those with PAH/SSD.[1,8] In a prospective, open, 12-week, randomized trial epoprostenol injection (n = 56) was compared with conventional therapy (n = 55). Most patients were either NYHA Functional Class III or Class IV, with the exception of five patients who were NYHA Functional Class II. Almost all patients were on anticoagulants; supplemental oxygen and diuretics were used by two-thirds of patients; oral vasodilators were used by 40% of patients; and one-third of patients were on digoxin. A statistically significant increase in cardiac index and significant decreases in mPAP, mRAP, and mean systemic arterial pressure (mSAP) after 12 weeks of treatment were noted in those receiving epoprostenol injection compared with those who did not. Clinically significant improvements in exercise capacity, as assessed by six-minute walk distance, were observed in patients given epoprostenol injection compared with patients given conventional therapy alone. Statistically significant improvements in dyspnea and fatigue, as evaluated by the Borg Dyspnea Index and Dyspnea Fatigue Index, were noted. At Week 12, NYHA Functional Class improved in 21 of 51 patients (41%) treated with epoprostenol injection compared with none of the 48 patients who only received conventional therapy.

Guidelines

In 2004, the American College of Chest Physicians (ACCP) developed evidence-based clinical practice guidelines regarding the screening, early detection, and diagnosis of PAH.[5] In patients with suspected pulmonary hypertension, right heart catheterization is required to confirm the presence of pulmonary hypertension, establish the specific diagnosis, and determine disease severity (grade A recommendation). In patients with suspected pulmonary hypertension, right heart catheterization is required to guide therapy (grade B recommendation).[5] The 2007 ACCP guidelines for medical therapy for PAH also restate these recommendations.[9]

In 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[4] The guidelines state that the diagnosis of PAH requires confirmation with a complete right heart catheterization. The hemodynamic definition of PAH is a mPAP greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of epoprostenol injection. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol injection as well as the monitoring required for adverse events and long-term efficacy, approval requires epoprostenol injection to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below. Specifically, approvals will remain at 14 days for patients currently receiving the agent with inadequate information or if the criteria are not met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoprostenol therapy is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1] for Patients not Currently Receiving Epoprostenol Therapy.** Approve if the patient meets the following criteria (A, B, C, D, and E):
   - **A)** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
   - **B)** The patient has had a right heart catheterization to confirm the diagnosis of PAH and the results of the right heart catheterization are as follows: mPAP > 25 mm Hg at rest; pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg; and pulmonary vascular resistance (PVR) > 3 Wood units; AND
   - **C)** The patient meets ONE of the following criteria (i or ii):
     - **i.** The patient is in Functional Class III or IV; OR
     - **ii.** The patient is in Functional Class II and meets ONE of the following criteria [1 or 2]:
       - **(1)** The patient has tried or is currently receiving one oral agent for PAH (e.g., Tracleer® [bosentan tablets], Letairis® [ambrisentan tablets], Opsumit® [macitentan tablets], Adempas® [riociguat tablets], Revatio®/Viagra® [sildenafil tablets], Adcirca®/Cialis® [tadalafil tablets]), or Orenitram™ [treprostinil extended-release tablets]); OR
         The patient is unable to take any of the agents above (e.g., those with liver abnormalities [Tracleer], women of childbearing potential [Tracleer, Letairis], concomitant use with nitrates [sildenafil, Adcirca/Cialis], hypotension, drug-drug interactions); OR
       - **(2)** The patient has tried one inhaled or parenteral prostacyclin product for PAH (e.g., Remodulin® [treprostinil injection], Ventavis® [iloprost inhalation solution], Tyvaso® [treprostinil inhalation solution]); AND
   - **D)** The patient has WHO Group 1 PAH; AND
   - **E)** Patients with idiopathic PAH must meet ONE of the following criteria (i, ii, iii, iv or v):
     - **i.** The patient has had an acute response to vasodilator testing that occurred during the right heart catheterization (defined as a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output) AND has tried one oral calcium channel blocker (CCB) therapy (e.g., amlodipine, nifedipine extended-release tablets); OR
     - **ii.** The patient did not have an acute response to vasodilator testing; OR
     - **iii.** The patient cannot undergo a vasodilator test; OR
     - **iv.** The patient cannot take CCB therapy (e.g., right heart failure, decreased cardiac output); OR
     - **v.** The patient has tried one CCB (e.g., amlodipine, nifedipine extended-release tablets).

Epoprostenol injection is indicated for the treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness include mainly patients with NYHA Functional Class III or IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.[1-3] Other agents used for the management of PAH (WHO Group 1) are recommended in patients in Functional Class II. The World Symposium on Pulmonary Hypertension (WSPH) updated treatment algorithm of PAH recommend intravenous epoprostenol for patients in WHO Functional Class III or Class IV.[16] Of note, continuous intravenous epoprostenol is recommended first-line for patients in Functional Class IV because of the survival benefit in this subset.[16] Patients in Functional Class II should be treated with an oral agent for PAH (e.g., Tracleer, Opsumit, Letairis, Adempas, sildenafil, Adcirca). ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend to perform a right heart catheterization in patients with

suspected pulmonary hypertension to confirm the presence of pulmonary hypertension, establish the diagnosis, and to determine disease severity.[5] An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, ATS and the Pulmonary Hypertension Association, notes all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to initiation of therapy.[4] The current hemodynamic definition of PAH is a mPAP greater than 25 mmHg; a PCWP, left atrial pressure, or LVEDP less than or equal to 15 mmHg; and a PVR greater than 3 Wood Units. Acute vasodilator testing should be done in all idiopathic PAH patients who might be considered potential candidates for long-term calcium channel blocker therapy. Those with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing. The definition of an acute responder is a reduction in mPAP to at least 10 mmHg or an absolute mPAP of less than 40 mmHg without a decrease in cardiac output.[4] Abrupt discontinuation or withdrawal of epoprostenol therapy should be avoided as patients may have symptoms associated with rebound pulmonary hypertension (e.g., dyspnea, dizziness) or other adverse consequences.[1] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

2. **Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1} for Patients Currently Receiving Epoprostenol Therapy.** Approve if the patient meets the following criteria (A or B):
   - **A)** The patient meets ALL of the following conditions (i, ii, and iii):
     - **i.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
     - **ii.** The patient has had a right heart catheterization to confirm the diagnosis of PAH and the results of the right heart catheterization are as follows: mPAP > 25 mm Hg at rest; PCWP ≤ 15 mm Hg; and PVR > 3 Wood units; AND
     - **iii.** The patient has WHO Group 1 PAH; OR
   - **B)** Approve a short-term supply of epoprostenol for up to 14 days if the patient does not meet the criteria in 2a above or if there is insufficient information available. Note: a 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of epoprostenol therapy may have severe adverse consequences.

Epoprostenol injection is indicated for the treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness include mainly patients with NYHA Functional Class III or IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.[1-3] ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend to perform a right heart catheterization in patients with suspected pulmonary hypertension to confirm the presence of pulmonary hypertension, establish the diagnosis, and to determine disease severity.[5] An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, ATS and the Pulmonary Hypertension Association, notes all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to initiation of therapy.[4] The current hemodynamic definition of PAH is an mPAP greater than 25 mmHg; a PCWP, left atrial pressure, or LVEDP less than or equal to 15 mmHg; and a PVR greater than 3 Wood Units. Abrupt discontinuation or withdrawal of epoprostenol therapy should be avoided as patients may have symptoms associated with rebound pulmonary hypertension (e.g., dyspnea, dizziness) or other adverse consequences.[1] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Other Uses with Supportive Evidence

3. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve if prescribed by, or in consultation with, a pulmonologist or a cardiologist.

   Although surgical pulmonary thromboendarterectomy (PTE) is the treatment of choice in symptomatic CTEPH, epoprostenol injection has been used with varying results to achieve hemodynamic stabilization prior to PTE.[10-14,18-19] Epoprostenol injection has been studied (retrospectively) as a therapeutic bridge between CTEPH diagnosis and surgical intervention. The 4th World Symposium on Pulmonary Hypertension published a paper that focused on non-PAH forms of pulmonary hypertension.[10] Final recommendations include that in severely compromised patients with surgically accessible disease but for whom surgery must be delayed, pre-operative medical therapy (e.g., prostanoids, endothelin receptor antagonists [ERAs] or phosphodiesterase type 5 [PDE5] inhibitors) may be used to improve hemodynamics and clinical performance before surgery. Preliminary data suggest that medications currently approved for PAH may have beneficial effects in patients with CTEPH, but as long as there are no robust data from randomized controlled trials, the decision of whether or not to treat CTEPH patients with these medications should be restricted to centers experienced in the management of the disease.[10] If surgery is not possible, only limited options are available for patients with CTEPH. The guidelines have not been updated since the approval of Adempas for CTEPH.[20] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

4. **Patients who are Currently Receiving Epoprostenol Therapy (for any Indication).** Approve a short-term supply of epoprostenol for up to 14 days if the patient does not meet any of the criteria above or if there is insufficient information available. Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of epoprostenol therapy may have severe adverse consequences.

   Abrupt discontinuation or withdrawal of epoprostenol therapy should be avoided as patients may have symptoms associated with rebound pulmonary hypertension (e.g., dyspnea, dizziness) or other adverse consequences.[1] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Epoprostenol injection (Flolan, Veletri, generics) has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Chronic Obstructive Pulmonary Disease (COPD) in a Patient Without PAH (WHO Group 1).** COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[15]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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OTHER REFERENCES UTILIZED

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
Integrated Policy	Integrated policy based on ESI West criteria	06/13/2012	--
Selected revision	Selected revision added to require a specialist physician be added to the criteria for CTEPH.	10/17/2012	--
Annual revision	--	06/19/2013	--
Annual revision	The approval duration for the following was changed from 6-month to 12-month intervals: patients with PAH WHO Group 1 who are not currently receiving epoprostenol therapy, patients with PAH (WHO Group 1) who are currently receiving epoprostenol therapy, and patients with CTEPH. For patients with PAH WHO Group 1 patients in Functional Class II (not currently receiving epoprostenol therapy), the criteria were changed to the patient has tried or is currently receiving one oral agent for PAH (or be unable to take any oral agents) or that the patient has tried one inhaled or parenteral prostacyclin product. Previous criteria required patients to try two other agents for PAH (which included both oral agents and inhaled agents for PAH) [or be unable to take all agents] or has tried Remodulin® (treprostinil injection). For patients with idiopathic PAH (WHO Group 1) [not currently receiving epoprostenol therapy], criteria were changed to list examples of reasons why patients may not be able to take CCB therapy (e.g., right heart failure, decreased cardiac output) instead of specifying that patients cannot take a CCB due to extreme right heart failure. Also, patients who have tried one oral CCB (examples listed) meet criteria and the specification "without vasodilator testing" was removed.	07/16/2014	08/04/2014
Selected revision	All approvals are provided for 3 years in duration unless otherwise noted below. Specifically, approvals will remain at 14 days for patients currently receiving the agent with inadequate information or if the criteria are not met.	09/03/2014	09/22/2014
Annual revision	No criteria changes.	08/05/2015	Previously in Effect
Selected revision	Removed the directive to refer cases to the medical director for review regarding patients who are currently receiving epoprostenol therapy (for any indication).	09/09/2015	10/01/2015

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; PAH – Pulmonary arterial hypertension WHO – World Health Organization; CTEPH – Chronic thromboembolic pulmonary hypertension.