

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VELETRI safely and effectively. See full prescribing information for VELETRI

VELETRI (epoprostenol for injection)

Initial US Approval: 1995

INDICATIONS AND USAGE

VELETRI is a prostanoid vasodilator indicated for:

- The long-term IV treatment of primary pulmonary hypertension (1)
- Pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy (1)

DOSAGE AND ADMINISTRATION

- Dosage
 - Infusion of VELETRI should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established. (2.1)
 - If symptoms of pulmonary hypertension persist or recur after improving - the infusion should be increased by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. (2.2)
- Administration
 - VELETRI is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. (2.3)
 - Do not mix with any other parenteral medications or solutions prior to or during administration. (2.4)
 - During initiation of treatment, VELETRI may be administered peripherally. (2.3)
- Reconstitution
 - Reconstituted in vial with only 5mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection. This solution may be refrigerated at 2°C to 8°C (36° to 46°F) for as long as 5 days or held at up to 25°C (77°F) for up to 48 hours prior to use. (2.4)
 - Reconstituted product should be further diluted as directed with the same diluent used for reconstitution. This solution may be used for up to 24 hours at room temperature. (Lower concentrations may be used with pump reservoir changed every 12 hours when used at room temperature). (2.4)
 - Solution for chronic delivery should be prepared in a drug delivery reservoir appropriate for the infusion pump (2.4).

DOSAGE FORMS AND STRENGTHS

1.5mg (1,500,000ng) VELETRI is in a 10mL vial with a red flip-off seal. (3)

CONTRAINDICATIONS

- Congestive heart failure due to severe left ventricular systolic dysfunction (4)
- Pulmonary edema (4)
- Hypersensitivity to the drug or to structurally related compounds (4)

WARNINGS AND PRECAUTIONS

- VELETRI should be used only by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. (5.1)
- Reconstitute only as directed, with Sterile Water for Injection or Sodium Chloride 0.9% Injection.(5.1)
- Do not abruptly lower the dose or withdraw dosing. All dosing initiation and changes should be closely monitored. (5.3, 5.4)

ADVERSE REACTIONS

- Most common adverse reactions during:
 - Dose Initiation and Escalation: Nausea, vomiting, headache, hypotension, flushing, chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia (6.1)
 - Chronic Dosing: Headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness (6.1)

To report SUSPECTED ADVERSE REACTIONS, please contact: ACTELION at 1-866-228-3546 or FDA at 1-800-FDA-1088, or <http://www.fda.gov/medwatch>

DRUG INTERACTIONS

- Diuretics, antihypertensive agents, or other vasodilators: reduction in blood pressure (7)
- Antiplatelet agents or anticoagulants: increase the risk of bleeding (7)
- Patients on digoxin: elevations of digoxin concentrations clinically significant in patients prone to digoxin toxicity (7)

See 8 for USE IN SPECIFIC POPULATIONS

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VELETRI is indicated for:

- the long-term intravenous treatment of primary pulmonary hypertension
- and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy
- [see *CLINICAL STUDIES: Clinical Trials in Pulmonary Hypertension (14.1)*].

2 DOSAGE AND ADMINISTRATION

Important Note: VELETRI must be reconstituted only as directed with Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Reconstituted solutions of VELETRI must not be diluted or administered with other parenteral solutions or medications [see *WARNINGS AND PRECAUTIONS: General (5.1)*].

2.1 Dosage

Continuous chronic infusion of VELETRI should be prepared as directed [see *Reconstitution (2.4)*], and administered through a central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Chronic infusion of VELETRI should be initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited or until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted [see *Dosage Adjustments (2.2)*]. If dose-limiting pharmacologic effects occur, then the infusion rate should be decreased to the point that the pharmacologic effects of VELETRI are tolerated. In clinical trials, the most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal pain, or respiratory disorder (most treatment-limiting adverse events were not serious). If the initial infusion rate of 2 ng/kg/min is not tolerated, use a lower dose.

In the controlled 12-week trial in PH/SSD, for example, the dose increased from a mean starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily to a mean dose of 4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks.

2.2 Dosage Adjustments

Changes in the chronic infusion rate should be based on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse events due to excessive doses of VELETRI. In general, increases in dose from the initial chronic dose should be expected.

Increments in dose should be considered if symptoms of pulmonary hypertension persist or recur after improving. The infusion should be increased by 1- to 2-ng/kg/min increments at

intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. In clinical trials, incremental increases in dose occurred at intervals of 24 to 48 hours or longer. Following establishment of a new chronic infusion rate, the patient should be observed, and standing and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During chronic infusion, the occurrence of dose-limiting pharmacological events may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of VELETRI or sudden large reductions in infusion rates should be avoided. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of VELETRI should be adjusted only under the direction of a physician.

In patients receiving lung transplants, doses of epoprostenol were tapered after the initiation of cardiopulmonary bypass.

2.3 Administration

VELETRI, once prepared as directed [see **Reconstitution (2.4)**], is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During initiation of treatment, VELETRI may be administered peripherally.

The ambulatory infusion pump used to administer VELETRI should: (1) be small and lightweight, (2) be able to adjust infusion rates in 2-ng/kg/min increments, (3) have occlusion, end-of-infusion, and low-battery alarms, (4) be accurate to $\pm 6\%$ of the programmed rate, and (5) be positive pressure-driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver VELETRI. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. The infusion pump used in the most recent clinical trials was the CADD-1 HFX 5100 (SIMS Deltec). A 60-inch microbore non-DEHP extension set with proximal antisiphon valve, low priming volume (0.9 mL), and in-line 0.22 micron filter was used during clinical trials.

To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets. A multi-lumen catheter should be considered if other intravenous therapies are routinely administered.

2.4 Reconstitution

VELETRI is stable only when reconstituted as directed using Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. VELETRI must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

Prior to use, VELETRI solutions reconstituted with 5 mL diluent must be protected from light and can be refrigerated at 2° to 8°C (36° to 46°F) for as long as 5 days or held at up to 25°C

(77°F) for up to 48 hours prior to use. **Do not freeze reconstituted solutions of VELETRI. Discard any reconstituted solution that has been frozen. Discard any reconstituted solution if it has been refrigerated for more than 5 days, or if held at room temperature for more than 48 hours.**

During use, a single reservoir of diluted solution of VELETRI prepared as directed can be administered at room temperature for up to 24 hours. (If lower concentrations are chosen, pump reservoirs should be changed every 12 hours when administered at room temperature.) Do not expose this solution to direct sunlight.

A concentration for the solution of VELETRI should be selected that is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed above. VELETRI, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump. Outlined in Table 1 are directions for preparing different concentrations of VELETRI for up to a 24-hour period.

Table 1: Reconstitution and Dilution Instructions

To make 100 mL of solution with Final Concentration (ng/mL) of:	Directions:
15,000 ng/mL*	Dissolve contents of one 1.5 mg vial with 5 mL of Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
30,000 ng/mL*	Dissolve contents of two 1.5 mg vials each with 5 mL of Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
* Higher concentrations may be prepared for patients who receive VELETRI long-term.	

Infusion rates may be calculated using the following formula:

$$\text{Infusion Rate (mL/hr)} = \frac{[\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 60 \text{ min/hr}]}{\text{Final Concentration (ng/mL)}}$$

Tables 2 and 3 provide infusion delivery rates for doses up to 16 ng/kg/min based upon patient weight, drug delivery rate, and concentration of the solution of VELETRI to be used. These tables may be used to select the most appropriate concentration of VELETRI that will result in

an infusion rate between the minimum and maximum flow rates of the infusion pump and that will allow the desired duration of infusion from a given reservoir volume. For infusion/dose rates lower than those listed in Tables 2 and 3, it is recommended that the pump rate be set by a healthcare professional such that steady state is achieved in the patient, keeping in mind the half life of epoprostenol is no more than six minutes. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of VELETRI. If lower concentrations are chosen, pump reservoirs should be changed every 12 hours when administered at room temperature.

Table 2: Infusion Rates for VELETRI at a Concentration of 15,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	---	---	---	---	1.0	1.1	1.3
30	---	---	1.0	1.2	1.4	1.7	1.9
40	---	1.0	1.3	1.6	1.9	2.2	2.6
50	---	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	4.5
80	1.3	1.9	2.6	3.2	3.8	4.5	5.1
90	1.4	2.2	2.9	3.6	4.3	5.0	5.8
100	1.6	2.4	3.2	4.0	4.8	5.6	6.4

Table 3: Infusion Rates for VELETRI at a Concentration of 30,000 ng/mL

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)					
	6	8	10	12	14	16
30	---	---	---	---	---	1.0
40	---	---	---	1.0	1.1	1.3
50	---	---	1.0	1.2	1.4	1.6
60	---	1.0	1.2	1.4	1.7	1.9
70	---	1.1	1.4	1.7	2.0	2.2
80	1.0	1.3	1.6	1.9	2.2	2.6
90	1.1	1.4	1.8	2.2	2.5	2.9
100	1.2	1.6	2.0	2.4	2.8	3.2

3 DOSAGE FORMS AND STRENGTHS

VELETRI contains epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol and is supplied as a sterile lyophilized material in a 10 mL vial with a red flip-off seal.

4 CONTRAINDICATIONS

A large study evaluating the effect of epoprostenol on survival in NYHA Class III and IV patients with congestive heart failure due to severe left ventricular systolic dysfunction was terminated after an interim analysis of 471 patients revealed a higher mortality in patients

receiving epoprostenol plus conventional therapy than in those receiving conventional therapy alone. The chronic use of VELETRI in patients with congestive heart failure due to severe left ventricular systolic dysfunction is therefore contraindicated.

Some patients with pulmonary hypertension have developed pulmonary edema during dose initiation, which may be associated with pulmonary veno-occlusive disease. VELETRI should not be used chronically in patients who develop pulmonary edema during dose initiation.

VELETRI is also contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

5 WARNINGS AND PRECAUTIONS

5.1 General

VELETRI must be reconstituted only as directed using Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. VELETRI must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration. [See *Reconstitution* (2.4)]

VELETRI should be used only by clinicians experienced in the diagnosis and treatment of pulmonary hypertension. The diagnosis of pulmonary hypertension should be carefully established.

5.2 Dose Initiation

VELETRI is a potent pulmonary and systemic vasodilator. Dose initiation with VELETRI must be performed in a setting with adequate personnel and equipment for physiologic monitoring and emergency care. Dose initiation in controlled PPH clinical trials was performed during right heart catheterization. In clinical trials, dose initiation was performed without cardiac catheterization. The risk of cardiac catheterization in patients with pulmonary hypertension should be carefully weighed against the potential benefits. During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output occurred rarely. In such cases, dose reduction should be considered, but such an increase does not imply that chronic treatment is contraindicated.

5.3 Chronic Use and Dose Adjustment

During chronic use, VELETRI is delivered continuously on an ambulatory basis through a permanent indwelling central venous catheter. Unless contraindicated, anticoagulant therapy should be administered to PPH and PH/SSD patients receiving VELETRI to reduce the risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale. In order to reduce the risk of infection, aseptic technique must be used in the reconstitution and administration of VELETRI as well as in routine catheter care. Because epoprostenol is metabolized rapidly, even brief interruptions in the delivery of VELETRI may result in symptoms associated with rebound pulmonary hypertension including dyspnea, dizziness, and

asthenia. The decision to initiate therapy with VELETRI should be based upon the understanding that there is a high likelihood that intravenous therapy with VELETRI will be needed indefinitely, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully considered.

Based on clinical trials, the acute hemodynamic response (reduction in pulmonary artery resistance) to epoprostenol did not correlate well with improvement in exercise tolerance or survival during chronic use of epoprostenol. Dosage of VELETRI during chronic use should be adjusted at the first sign of recurrence or worsening of symptoms attributable to pulmonary hypertension or the occurrence of adverse events associated with epoprostenol [see ***DOSAGE AND ADMINISTRATION (2)***]. Following dosage adjustments, standing and supine blood pressure and heart rate should be monitored closely for several hours.

5.4 Withdrawal Effects

Abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage of VELETRI may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness, and asthenia. In clinical trials, one Class III primary pulmonary hypertension patient's death was judged attributable to the interruption of epoprostenol. Abrupt withdrawal should be avoided.

5.5 Sepsis

See ***ADVERSE REACTIONS, Adverse Events Attributable to the Drug Delivery System (6.1)***.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical trials, adverse events were classified as follows: (1) adverse events during dose initiation and escalation, (2) adverse events during chronic dosing, and (3) adverse events associated with the drug delivery system.

Adverse Events During Dose Initiation and Escalation

During early clinical trials, epoprostenol was increased in 2-ng/kg/min increments until the patients developed symptomatic intolerance. The most common adverse events and the adverse events that limited further increases in dose were generally related to vasodilation, the major pharmacologic effect of epoprostenol. The most common dose-limiting adverse events (occurring in $\geq 1\%$ of patients) were nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain,

musculoskeletal pain, and tachycardia. Table 4 lists the adverse events reported during dose initiation and escalation in decreasing order of frequency.

Table 4: Adverse Events During Dose Initiation and Escalation

Adverse Events Occurring in \geq1% of Patients	Epoprostenol (n = 391)
Flushing	58%
Headache	49%
Nausea/vomiting	32%
Hypotension	16%
Anxiety, nervousness, agitation	11%
Chest pain	11%
Dizziness	8%
Bradycardia	5%
Abdominal pain	5%
Musculoskeletal pain	3%
Dyspnea	2%
Back pain	2%
Sweating	1%
Dyspepsia	1%
Hypesthesia/paresthesia	1%
Tachycardia	1%

Adverse Events During Chronic Administration for PPH

Interpretation of adverse events is complicated by the clinical features of PPH and PH/SSD, which are similar to some of the pharmacologic effects of epoprostenol (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, edema, hypoxia, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to epoprostenol. These include headache, jaw pain, flushing, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness.

In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 5 lists adverse events that occurred at a rate at least 10% different in the 2 groups in controlled trials for PPH.

Table 5: Adverse Events Regardless of Attributions Occurring in Patients With PPH With $\geq 10\%$ Difference Between Epoprostenol and Conventional Therapy Alone

Adverse Event	Epoprostenol (n = 52)	Conventional Therapy (n = 54)
Occurrence More Common With Epoprostenol		
General		
Chills/fever/sepsis/flu-like symptoms	25%	11%
Cardiovascular		
Tachycardia	35%	24%
Flushing	42%	2%
Gastrointestinal		
Diarrhea	37%	6%
Nausea/vomiting	67%	48%
Musculoskeletal		
Jaw pain	54%	0%
Myalgia	44%	31%
Nonspecific musculoskeletal pain	35%	15%
Neurological		
Anxiety/nervousness/tremor	21%	9%
Dizziness	83%	70%
Headache	83%	33%
Hypesthesia, hyperesthesia, paresthesia	12%	2%
Occurrence More Common With Standard Therapy		
Cardiovascular		
Heart failure	31%	52%
Syncope	13%	24%
Shock	0%	13%
Respiratory		
Hypoxia	25%	37%

Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving epoprostenol.

Table 6 lists additional adverse events reported in PPH patients receiving epoprostenol plus conventional therapy or conventional therapy alone during controlled clinical trials.

Table 6: Adverse Events Regardless of Attribution Occurring In Patients with PPH With <10% Difference between Epoprostenol and Conventional Therapy

Adverse Event	Epoprostenol (n = 52)	Conventional Therapy (n = 54)
General		
Asthenia	87%	81%
Cardiovascular		
Angina pectoris	19%	20%
Arrhythmia	27%	20%
Bradycardia	15%	9%
Supraventricular tachycardia	8%	0%
Pallor	21%	30%
Cyanosis	31%	39%
Palpitation	63%	61%
Cerebrovascular accident	4%	0%
Hemorrhage	19%	11%
Hypotension	27%	31%
Myocardial ischemia	2%	6%
Gastrointestinal		
Abdominal Pain	27%	31%
Anorexia	25%	30%
Ascites	12%	17%
Constipation	6%	2%
Metabolic		
Edema	60%	63%
Hypokalemia	6%	4%
Weight reduction	27%	24%
Weight gain	6%	4%
Musculoskeletal		
Arthralgia	6%	0%
Bone pain	0%	4%
Chest pain	67%	65%
Neurological		
Confusion	6%	11%
Convulsion	4%	0%
Depression	37%	44%

Adverse Event	Epoprostenol (n = 52)	Conventional Therapy (n = 54)
Insomnia	4%	4%
Respiratory		
Cough increase	38%	46%
Dyspnea	90%	85%
Epistaxis	4%	2%
Pleural effusion	4%	2%
Skin and Appendages		
Pruritus	4%	0%
Rash	10%	13%
Sweating	15%	20%
Special Senses		
Amblyopia	8%	4%
Vision abnormality	4%	0%

Adverse Events During Chronic Administration for PH/SSD

In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 7 lists adverse events that occurred at a rate at least 10% different in the 2 groups in the controlled trial for patients with PH/SSD.

Table 7: Adverse Events Regardless of Attribution Occurring in Patients With PH/SSD With $\geq 10\%$ Difference Between Epoprostenol and Conventional Therapy Alone

Adverse Event	Epoprostenol (n = 56)	Conventional Therapy (n = 55)
Occurrence More Common With Epoprostenol		
Cardiovascular		
Flushing	23%	0%
Hypotension	13%	0%
Gastrointestinal		
Anorexia	66%	47%
Nausea/vomiting	41%	16%
Diarrhea	50%	5%
Musculoskeletal		
Jaw pain	75%	0%
Pain/neck pain/arthritis	84%	65%
Neurological		
Headache	46%	5%
Skin and Appendages		
Skin ulcer	39%	24%
Eczema/rash/urticaria	25%	4%
Occurrence More Common With Conventional Therapy		
Cardiovascular		
Cyanosis	54%	80%
Pallor	32%	53%
Syncope	7%	20%
Gastrointestinal		
Ascites	23%	33%
Esophageal reflux/gastritis	61%	73%
Metabolic		
Weight decrease	45%	56%
Neurological		
Dizziness	59%	76%
Respiratory		
Hypoxia	55%	65%

Table 8 lists additional adverse events reported in PH/SSD patients receiving epoprostenol plus conventional therapy or conventional therapy alone during controlled clinical trials.

Table 8: Adverse Events Regardless of Attribution Occurring in Patients With PH/SSD With <10% Difference Between Epoprostenol and Conventional Therapy Alone

Adverse Event*	Epoprostenol (n = 56)	Conventional Therapy (n = 55)
General Asthenia Hemorrhage/hemorrhage injection site/hemorrhage rectal Infection/rhinitis Chills/fever/sepsis/flu-like symptoms	100% 11% 21% 13%	98% 2% 20% 11%
Blood and Lymphatic Thrombocytopenia	4%	0%
Cardiovascular Heart failure/heart failure right Myocardial Infarction Palpitation Shock Tachycardia Vascular disorder peripheral Vascular disorder	11% 4% 63% 5% 43% 96% 95%	13% 0% 71% 5% 42% 100% 89%
Gastrointestinal Abdominal enlargement Abdominal pain Constipation Flatulence	4% 14% 4% 5%	0% 7% 2% 4%
Metabolic Edema/edema peripheral/edema genital Hypercalcemia Hyperkalemia Thirst	79% 48% 4% 0%	87% 51% 0% 4%
Musculoskeletal Arthritis Back pain Chest pain Cramps leg	52% 13% 52% 5%	45% 5% 45% 7%
Respiratory Cough increase	82%	82%

Adverse Event*	Epoprostenol (n = 56)	Conventional Therapy (n = 55)
Dyspnea	100%	100%
Epistaxis	9%	7%
Pharyngitis	5%	2%
Pleural effusion	7%	0%
Pneumonia	5%	0%
Pneumothorax	4%	0%
Pulmonary edema	4%	2%
Respiratory disorder	7%	4%
Neurological		
Anxiety/hyperkinesia/nervousness/tremor	7%	5%
Depression/depression psychotic	13%	4%
Hyperesthesia/hypesthesia/paresthesia	5%	0%
Insomnia	9%	0%
Somnolence	4%	2%
Skin and Appendages		
Collagen disease	82%	84%
Pruritus	4%	2%
Sweat	41%	36%
Urogenital		
Hematuria	5%	0%
Urinary tract infection	7%	0%
*Adverse events that occurred in at least 2 patients in either treatment group.		

Although the relationship to epoprostenol administration has not been established, pulmonary embolism has been reported in several patients taking epoprostenol and there have been reports of hepatic failure.

Adverse Events Attributable to the Drug Delivery System

Chronic infusions of epoprostenol are delivered using a small, portable infusion pump through an indwelling central venous catheter. During controlled PPH trials of up to 12 weeks' duration, up to 21% of patients reported a local infection and up to 13% of patients reported pain at the injection site. During a controlled PH/SSD trial of 12 weeks' duration, 14% of patients reported a local infection and 9% of patients reported pain at the injection site. During long-term follow-up in the clinical trial of PPH, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.32 infections/patient per year in patients treated with epoprostenol. This rate was higher than reported in patients using chronic indwelling central venous catheters to administer parenteral nutrition, but lower than reported in oncology

patients using these catheters. Malfunctions in the delivery system resulting in an inadvertent bolus of or a reduction in epoprostenol were associated with symptoms related to excess or insufficient epoprostenol, respectively [see *ADVERSE REACTIONS, Clinical Trials Experience, Adverse Events During Chronic Administration for PPH (6.1)*].

6.2 Post-Marketing Experience

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of epoprostenol. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to epoprostenol.

Blood and Lymphatic: Anemia, hypersplenism, pancytopenia, splenomegaly.

Endocrine and Metabolic: Hyperthyroidism

7 DRUG INTERACTIONS

Additional reductions in blood pressure may occur when VELETRI is administered with diuretics, antihypertensive agents, or other vasodilators. When other antiplatelet agents or anticoagulants are used concomitantly, there is the potential for VELETRI to increase the risk of bleeding. However, patients receiving infusions of epoprostenol in clinical trials were maintained on anticoagulants without evidence of increased bleeding. In clinical trials, epoprostenol was used with digoxin, diuretics, anticoagulants, oral vasodilators, and supplemental oxygen.

In a pharmacokinetic substudy in patients with congestive heart failure receiving furosemide or digoxin in whom therapy with epoprostenol was initiated, apparent oral clearance values for furosemide (n = 23) and digoxin (n = 30) were decreased by 13% and 15%, respectively, on the second day of therapy and had returned to baseline values by day 87. The change in furosemide clearance value is not likely to be clinically significant. However, patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with epoprostenol, which may be clinically significant in patients prone to digoxin toxicity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproductive studies have been performed in pregnant rats and rabbits at doses up to 100 mcg/kg/day (600 mcg/m²/day in rats, 2.5 times the recommended human dose, and 1,180 mcg/m²/day in rabbits, 4.8 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to epoprostenol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

The use of VELETRI during labor, vaginal delivery, or cesarean section has not been adequately studied in humans.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when VELETRI is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of epoprostenol in pulmonary hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Signs and symptoms of excessive doses of epoprostenol during clinical trials are the expected dose-limiting pharmacologic effects of epoprostenol, including flushing, headache, hypotension, tachycardia, nausea, vomiting, and diarrhea. Treatment will ordinarily require dose reduction of epoprostenol.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of epoprostenol. The patient vomited and became unconscious with an initially unrecordable blood pressure. Epoprostenol was discontinued and the patient regained consciousness within seconds. In clinical practice, fatal occurrences of hypoxemia, hypotension, and respiratory arrest have been reported following overdosage of epoprostenol.

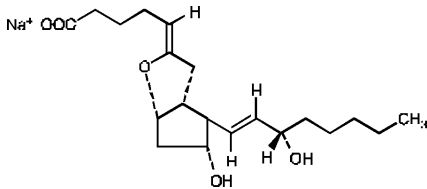
Single intravenous doses of epoprostenol at 10 and 50 mg/kg (2,703 and 27,027 times the recommended acute phase human dose based on body surface area) were lethal to mice and rats, respectively. Symptoms of acute toxicity were hypoactivity, ataxia, loss of righting reflex, deep slow breathing, and hypothermia.

11 DESCRIPTION

Epoprostenol sodium is a sterile sodium salt formulated for intravenous (IV) administration. Each vial of VELETRI contains epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol, 50 mg arginine, and 50 mg mannitol. Sodium hydroxide is added to adjust pH.

Epoprostenol (PGI₂, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

Epoprostenol is (5*Z*,9*a*,11*a*,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid. Epoprostenol sodium has a molecular weight of 374.45 and a molecular formula of C₂₀H₃₁NaO₅. The structural formula is:



VELETRI is a white to off-white lyophilized material that may be translucent. It is reconstituted with Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP.

The reconstituted solution of VELETRI has a pH of >11.0 and is increasingly unstable at a lower pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Epoprostenol has 2 major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right- and left-ventricular afterload and increase cardiac output and stroke volume. The effect of epoprostenol on heart rate in animals varies with dose. At low doses, there is vagally mediated bradycardia, but at higher doses, epoprostenol causes reflex tachycardia in response to direct vasodilation and hypotension. No major effects on cardiac conduction have been observed. Additional pharmacologic effects of epoprostenol in animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying.

12.3 Pharmacokinetics

Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzymatic degradation. Animal studies using tritium-labeled epoprostenol have indicated a high clearance (93 mL/kg/min), small volume of distribution (357 mL/kg), and a short half-life (2.7 minutes). During infusions in animals, steady-state plasma concentrations of tritium-labeled epoprostenol were reached within 15 minutes and were proportional to infusion rates.

No available chemical assay is sufficiently sensitive and specific to assess the *in vivo* human pharmacokinetics of epoprostenol. The *in vitro* half-life of epoprostenol in human blood at 37°C and pH 7.4 is approximately 6 minutes; therefore, the *in vivo* half-life of epoprostenol in humans is expected to be no greater than 6 minutes. The *in vitro* pharmacologic half-life of epoprostenol in human plasma, based on inhibition of platelet aggregation, was similar for males (n = 954) and females (n = 1,024).

Tritium-labeled epoprostenol has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is metabolized to 2 primary metabolites: 6-keto-PGF_{1α} (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF_{1α} (enzymatically formed), both of which have pharmacological activity orders of magnitude less than epoprostenol in animal test systems. The recovery of radioactivity in urine and feces over a 1-week period was 82% and 4% of the administered dose, respectively. Fourteen additional minor metabolites have been isolated from urine, indicating that epoprostenol is extensively metabolized in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis and Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. A micronucleus test in rats revealed no evidence of mutagenicity. The Ames test and DNA elution tests were also negative, although the instability of epoprostenol makes the significance of these tests uncertain. Fertility was not impaired in rats given epoprostenol by subcutaneous injection at doses up to 100 mcg/kg/day (600 mcg/m²/day, 2.5 times the recommended human dose [4.6 ng/kg/min or 245.1 mcg/m²/day, IV] based on body surface area).

14 CLINICAL STUDIES

14.1 Clinical Trials in Pulmonary Hypertension

Acute Hemodynamic Effects: Acute intravenous infusions of epoprostenol for up to 15 minutes in patients with secondary and primary pulmonary hypertension produce dose-related increases in cardiac index (CI) and stroke volume (SV) and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure (SAPm). The effects of epoprostenol on mean pulmonary arterial pressure (PAPm) were variable and minor.

Chronic Infusion in Primary Pulmonary Hypertension (PPH):

Hemodynamic Effects: Chronic continuous infusions of epoprostenol in patients with PPH were studied in 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing epoprostenol plus conventional therapy to conventional therapy alone. Dosage of epoprostenol was determined as described in **DOSAGE AND ADMINISTRATION (2)** and averaged 9.2 ng/kg/min at study's end. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all

patients were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are described.

Chronic hemodynamic effects were generally similar to acute effects. Increases in CI, SV, and arterial oxygen saturation and decreases in PAPm, mean right atrial pressure (RAPm), TPR, and systemic vascular resistance (SVR) were observed in patients who received epoprostenol chronically compared to those who did not. Table 9 illustrates the treatment-related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

Table 9: Hemodynamics During Chronic Administration of Epoprostenol in Patients With PPH

Hemodynamic Parameter	Baseline		Mean Change from Baseline at End of Treatment Period*	
	Epoprostenol (N = 52)	Standard Therapy (N = 54)	Epoprostenol (N = 48)	Standard Therapy (N = 41)
CI (L/min/m ²)	2.0	2.0	0.3†	-0.1
PAPm (mm Hg)	60	60	-5†	1
PVR (Wood U)	16	17	-4†	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6†	-1
TPR (Wood U)	20	21	-5†	1

* At 8 weeks: Epoprostenol N = 10, conventional therapy N = 11 (N is the number of patients with hemodynamic data).

At 12 weeks: Epoprostenol N = 38, conventional therapy N = 30 (N is the number of patients with hemodynamic data).

† Denotes statistically significant difference between Epoprostenol and conventional therapy groups. CI = cardiac index, PAPm = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure, SV = stroke volume, TPR = total pulmonary resistance.

These hemodynamic improvements appeared to persist when epoprostenol was administered for at least 36 months in an open, nonrandomized study.

Clinical Effects: Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk test in patients receiving continuous intravenous epoprostenol plus conventional therapy (N = 52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N = 54). Improvements were apparent as early as the first week of therapy.

Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index.

Survival was improved in NYHA functional Class III and Class IV PPH patients treated with epoprostenol for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period, 8 of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died ($p = 0.003$).

Chronic Infusion in Pulmonary Hypertension Associated with the Scleroderma Spectrum of Diseases (PH/SSD):

Hemodynamic Effects: Chronic continuous infusions of epoprostenol in patients with PH/SSD were studied in a prospective, open, randomized trial of 12 weeks' duration comparing epoprostenol plus conventional therapy (N = 56) to conventional therapy alone (N = 55). Except for 5 NYHA functional Class II patients, all patients were either functional Class III or Class IV. Dosage of epoprostenol was determined as described in **DOSAGE AND ADMINISTRATION (2)** and averaged 11.2 ng/kg/min at study's end. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. A statistically significant increase in CI, and statistically significant decreases in PAPm, RAPm, PVR, and SAPm after 12 weeks of treatment were observed in patients who received epoprostenol chronically compared to those who did not. Table 10 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

Table 10: Hemodynamics During Chronic Administration of Epoprostenol in Patients With PH/SSD

Hemodynamic Parameter	Baseline		Mean Change from Baseline at 12 Weeks	
	Epoprostenol (N = 56)	Conventional Therapy (N = 55)	Epoprostenol (N = 50)	Conventional Therapy (N = 48)
CI (L/min/m ²)	1.9	2.2	0.5*	-0.1
PAPm (mm Hg)	51	49	-5*	1
RAPm (mm Hg)	13	11	-1*	1
PVR (Wood U)	14	11	-5*	1
SAPm (mm Hg)	93	89	-8*	-1

* Denotes statistically significant difference between Epoprostenol and conventional therapy groups (N is the number of patients with hemodynamic data).
 CI = cardiac index, PAPm = mean pulmonary arterial pressure, RAPm = mean right atrial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure.

Clinical Effects: Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk, in patients receiving continuous intravenous epoprostenol plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by the Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol and 13/48 (27%) with conventional therapy alone worsened. Of the patients randomized, NYHA functional class data at 12 weeks were not available for 5 patients treated with epoprostenol and 7 patients treated with conventional therapy alone.

No statistical difference in survival over 12 weeks was observed in PH/SSD patients treated with epoprostenol as compared to those receiving conventional therapy alone. At the end of the treatment period, 4 of 56 (7%) patients receiving epoprostenol died, whereas 5 of 55 (9%) patients receiving conventional therapy alone died.

No controlled clinical trials with epoprostenol have been performed in patients with pulmonary hypertension associated with other diseases.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

VELETRI is supplied as a sterile lyophilized material in 10 mL vials each with a red flip-off seal.

Each 10 mL vial containing epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng) epoprostenol, is packaged in carton of 1 vial (NDC 66215-401-01).

Store the vials of VELETRI at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light.

16.2 Storage and Stability

Unopened vials of VELETRI are stable until the date indicated on the package when stored at 20° to 25°C (68° to 77°F) and protected from light in the carton.

Prior to use, VELETRI solutions reconstituted with 5 mL diluent must be protected from light and can be refrigerated at 2° to 8°C (36° to 46°F) for as long as 5 days or held at up to 25°C (77°F) for up to 48 hours prior to use. **Do not freeze reconstituted solutions of VELETRI. Discard any reconstituted solution that has been frozen. Discard any reconstituted solution if it has been refrigerated for more than 5 days, or if held at room temperature for more than 48 hours.**

When the patient is then ready for the administration at room temperature, the dosing solutions may be prepared from the 5 mL solution as directed, by dilution with the same appropriate diluent to the needed concentration. This fully diluted solution can then be administered at room temperature for periods up to 24 hours. (If lower concentrations are chosen, the pump reservoirs should be changed every 12 hours when administered at room temperature.) Do not expose this solution to direct sunlight. [See **Reconstitution (2.4)**].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, VELETRI should not be administered.

17 PATIENT COUNSELING INFORMATION

Patients receiving VELETRI should receive the following information.

VELETRI must be reconstituted as directed using only Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. VELETRI is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with VELETRI requires commitment by the patient to drug reconstitution, drug administration, and care of the permanent central venous catheter. Sterile technique must be adhered to in preparing the drug and in the care of the catheter, and even brief interruptions in the delivery of VELETRI may result in rapid symptomatic deterioration. A patient's decision to receive VELETRI should be based upon the understanding that there is a high likelihood that therapy with VELETRI will be needed for prolonged periods, possibly years. The patient's ability to accept and care for a permanent intravenous catheter and infusion pump should also be carefully considered.

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