PRODUCT MONOGRAPH

# [Pr]Epoprostenol for Injection

Epoprostenol Sodium
0.5 mg or 1.5 mg per vial

**Vasodilator**

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## ACTION AND CLINICAL PHARMACOLOGY

Epoprostenol sodium, also known as prostacyclin, $PGI_2$ or PGX, a metabolite of arachidonic acid, is a naturally occurring prostaglandin. Epoprostenol has two major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation. In animals, the vasodilatory effects of epoprostenol 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.

### Pharmacokinetics

**Absorption/Distribution:** Epoprostenol is rapidly hydrolyzed at neutral blood pH and is also subject to enzymatic degradation. No available chemical assay is sufficiently sensitive and specific to assess the *in vivo* human pharmacokinetics of epoprostenol. Animal studies using tritium-labelled epoprostenol have indicated a high clearance (93 mL/min/kg), 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-labelled epoprostenol were reached within 15 minutes and were proportional to infusion rates.

**Metabolism:** Tritium-labelled epoprostenol has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is metabolized to 6-keto-$PGF_{1\alpha}$ (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro- $PGF_{1\alpha}$ (enzymatically formed), both of which have pharmacological activity at orders of magnitude less than epoprostenol in animal test systems. The recovery of radioactivity in urine and feces over a one-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.

**Elimination:** The *in vitro* half-life of epoprostenol in human blood at 37°C and pH 7.4 is approximately 6 minutes; the *in vivo* half-life of epoprostenol in humans is therefore 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, is 10.6 minutes in males (N=954) and 10.8 minutes in females (N=1024).

### Pharmacodynamics

**Acute Hemodynamic Effects of Epoprostenol in Pulmonary Arterial Hypertension (PAH):** Acute intravenous infusions of epoprostenol for up to 15 minutes in patients with idiopathic or heritable PAH or PAH associated with Scleroderma Spectrum of Diseases (PAH/SSD) produced

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 Hemodynamic Effects of Epoprostenol in Idiopathic or Heritable PAH:** Chronic hemodynamic effects were generally similar to acute effects. CI, SV, and arterial oxygen saturation were increased, and PAPm, right atrial pressure (RAP), TPR, and systemic vascular resistance (SVR) were decreased in patients who received epoprostenol chronically, compared to those who did not.

Survival was improved in New York Heart Association (NYHA) functional Class III and Class IV patients with idiopathic or heritable PAH treated with epoprostenol for 12 weeks in a multicenter, open, randomized, parallel, controlled study. At the end of the treatment period, 8 of 40 patients receiving standard therapy alone had died, whereas none of the 41 patients receiving epoprostenol had died (p=0.003).

Table 1 illustrates the treatment related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

**Table 1**: **Hemodynamics During Chronic Administration of Intravenous Infusions of Epoprostenol in Patients with Idiopathic or Heritable PAH**

| Hemodynamic Parameter | Baseline | | Mean Change from Baseline at End of Treatment Period* | |
|---|---|---|---|---|
| | Epoprostenol sodium (N=52) | Conventional Therapy (N=54) | Epoprostenol sodium (N=48) | Conventional 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 Sodium N=10; Conventional Therapy N=11 (N is the number of patients with hemodynamic data).
At 12 weeks: Epoprostenol Sodium N=38; Conventional Therapy N=30 (N is the number of patients with hemodynamic data).

** Denotes statistically significant difference between Epoprostenol Sodium and Conventional Therapy groups Cl = cardiac index; PAPm = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SAPm = mean systemic arterial pressure; SV = stroke volume ; TPR = total pulmonary resistance.

**Chronic Infusion in PAH/SSD : Hemodynamic Effects:** Chronic continuous infusions of epoprostenol in patients with PAH/SSD were studied in a prospective, open, randomized trial of 12-weeks duration comparing epoprostenol plus conventional therapy to conventional therapy alone. Except for the five NYHA functional Class II patients, all patients were either functional Class III or Class IV. The patients principally had pulmonary vascular manifestations of the collagen-vascular disease, with minimal evidence of interstitial lung disease and with total lung capacities greater than 60% of the predicted normal. Dosage of epoprostenol was determined as described in DOSAGE AND ADMINISTRATION and averaged 11.2 ng/kg per minute at study

end. Conventional therapy varied among patients and included 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, RAP, PVR, and SAPm were observed in patients who received epoprostenol chronically compared to those who did not. Table 2 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

**Table 2: Hemodynamics During Chronic Administration of Intravenous Infusions of Epoprostenol in Patients with PAH/SSD**

| Hemodynamic Parameter | Baseline | | Mean Change from Baseline at 12 Weeks | |
|---|---|---|---|---|
| | Epoprostenol Sodium (N=56) | Conventional Therapy (N=55) | Epoprostenol Sodium (N=50) | Conventional Therapy (N=48) |
| PAPm (mm/Hg) | 51 | 49 | -5* | 1 |
| RAP (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 Sodium and Conventional Therapy groups (N is the number of patients with hemodynamic data)

CI = Cardiac index; PAPm = mean pulmonary arterial pressure; RAP = 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 administration of epoprostenol plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Improvements were apparent as early as 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. By 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.

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

## INDICATIONS AND CLINICAL USE

Epoprostenol for Injection (epoprostenol sodium) is indicated for the long-term intravenous treatment of idiopathic or heritable pulmonary arterial hypertension (PAH) or PAH associated with connective tissue diseases (CTD) in patients with WHO Functional Class III-IV symptoms who did not respond adequately to conventional therapy.

Prior to initiation of therapy, the potential benefit of Epoprostenol for Injection should be weighed against the risks associated with use of the drug and the presence of an indwelling central venous catheter.

Epoprostenol for Injection should be used only by clinicians experienced in the diagnosis and treatment of PAH. The diagnosis of idiopathic or heritable PAH or PAH/CTD should be carefully established by standard clinical tests.

## CONTRAINDICATIONS

**The chronic use of Epoprostenol for Injection (epoprostenol sodium) in patients with congestive heart failure (CHF) due to severe left ventricular systolic dysfunction is contraindicated.** A large study evaluating the effect of epoprostenol on survival in NYHA Class III and IV patients with CHF 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.

Epoprostenol for Injection is also contraindicated in patients with known or suspected hypersensitivity to the drug or any of its excipients, or to structurally-related compounds.

Epoprostenol for Injection should not be used chronically in patients who develop pulmonary edema during dose initiation.

## WARNINGS

**Epoprostenol for Injection (epoprostenol sodium) must be reconstituted only as directed using specific STERILE DILUENT for Epoprostenol for Injection. Epoprostenol for Injection must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.**

**Epoprostenol for Injection is not to be used for bolus administration (see ADVERSE EVENTS, Adverse Events during Acute Dose Escalation).**

**Abrupt Withdrawal:** Abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage of epoprostenol may result in symptoms associated with rebound PAH, including dyspnea, dizziness, and asthenia and may lead to death. In clinical trials, there were rare reports of deaths considered attributable to the interruption of epoprostenol. Abrupt withdrawal should be avoided, except in life-threatening situations (e.g. unconsciousness, collapse, etc.).

**Pulmonary Edema:** A minority of patients have PAH associated with pulmonary veno-occlusive disease. Some of these patients develop pulmonary edema during dose initiation. Where pulmonary edema arises within hours to days of starting epoprostenol infusion, a diagnosis of veno-occlusive disease should be considered. In such cases consideration should be given to discontinuation of epoprostenol. Epoprostenol should be discontinued after dose tapering.

Epoprostenol should not be used chronically in patients who develop pulmonary edema during

dose initiation.

**Sepsis:** Sepsis/septicemia is a known risk associated with the presence of an indwelling central venous catheter and requires immediate access to expert medical care (see ADVERSE REACTIONS, Adverse Events Attributable to the Drug Delivery System).

## PRECAUTIONS

Epoprostenol for Injection (epoprostenol sodium) is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 minutes of the end of administration. Acute dose initiation with epoprostenol must be performed in a hospital setting with adequate personnel and equipment for physiologic monitoring and emergency care.

Epoprostenol is a potent inhibitor of platelet aggregation, therefore, an increased risk for hemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding (see Risk of Bleeding and Drug Interactions).

Because of the high pH of the final infusion solutions, care should be taken to avoid extravasation during their administration and consequent risk of tissue damage.

During the early phase of chronic administration, intense patient education is required.

Due to the potential for problems associated with the drug delivery system, immediate access to medical care should be available during chronic treatment.

Epoprostenol is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with epoprostenol requires commitment by the patient to drug reconstitution, drug administration, care of the permanent central venous catheter, and access to intense and ongoing patient education. 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 epoprostenol may result in rapid symptomatic deterioration. The decision to receive epoprostenol for PAH should be based upon the understanding that there is a high likelihood that therapy with epoprostenol will be needed for prolonged periods, possibly years, 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 to epoprostenol did not correlate well with survival during chronic use of epoprostenol. Dosage of epoprostenol during chronic use should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PAH, or the occurrence of adverse events associated with epoprostenol (see DOSAGE AND ADMINISTRATION). During administration and following dosage adjustments, standing and supine blood pressure and heart rate should be monitored closely for several hours.

During ongoing treatment, patients should avoid situations which promote vasodilation such as saunas, hot baths and sunbathing. Severe hypotension has been seen in patients treated with

chronic epoprostenol infusions under such circumstances.

Epoprostenol use has been associated with an increased incidence of bradycardia in patients with PAH and with episodes of severe hypotension, including fatalities.

Elevated serum glucose levels have been reported.

If excessive hypotension occurs during administration of epoprostenol the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness (see OVERDOSAGE).

The sterile diluent contains no preservative; consequently a vial should be used once only and then discarded.

**Risk of Bleeding**
Prothrombin times should be monitored because anticoagulant therapy is generally recommended in these patients. Platelet counts should also be monitored.

**Drug Interactions**
Additional reductions in blood pressure may occur when epoprostenol is administered with diuretics, antihypertensive agents, or other vasodilators. When NSAIDs or other drugs affecting platelet aggregation are used concomitantly, there is the potential for epoprostenol to increase the risk of bleeding. In clinical trials, epoprostenol was used with digoxin, diuretics, anticoagulants, oral vasodilators and supplemental oxygen.

The vasodilator effects of epoprostenol may augment or be augmented by concomitant use of other vasodilators.

In a pharmacokinetic substudy in patients with congestive heart failure receiving furosemide or digoxin in whom epoprostenol therapy 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 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.

**Fertility**
Animal studies did not indicate harmful effects with respect to fertility. However, the relevance of these findings in humans is unknown (see TOXICOLOGY).

**Use in Pregnancy**
There are no adequate and well-controlled studies in pregnant women. Animal studies did not indicate harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. However, the relevance of these findings in humans is unknown (see TOXICOLOGY).

**Labour and Delivery**
The use of epoprostenol during labour, vaginal delivery, or cesarean section has not been studied in humans.

**Use in Nursing Mothers**
It is not known whether epoprostenol or its metabolites are excreted in human milk. A risk to the nursing child cannot be excluded. Because many drugs are excreted in human milk, consideration should be given to discontinuation of breast feeding when epoprostenol is to be administered to a nursing woman or to discontinue/abstain from epoprostenol therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

**Pediatric Use**
The safety and effectiveness of epoprostenol in children has not been established.

**Geriatric Use**
Clinical studies of epoprostenol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

**Ability to Perform Tasks that Require Judgement, Motor or Cognitive Skills**
PAH and its therapeutic management may affect the ability to drive and operate machinery.

## ADVERSE REACTIONS

**During Clinical Trials, Adverse Events were Classified as Follows:** (1) adverse events during dose escalation, (2) adverse events during chronic dosing, and (3) adverse events associated with the drug delivery system.

**Adverse Events during Dose Escalation**
In early clinical trials, epoprostenol sodium was increased in 2 ng/kg/min increments until such time as the patients developed symptomatic intolerance. The most common adverse events and those that limited further increases in dose were generally related to the major pharmacologic effect of epoprostenol, i.e. vasodilation. Table 3 lists the adverse events reported during dose escalation in decreasing order of frequency as well as the percent of cases where the event was dose limiting. Age-related differences (< 16 vs ≥ 16 years) in the incidence of adverse events are shown in Table 4.

**Table 3 : Adverse Events During Dose Escalation**

| **Adverse Events Occurring in ≥ 1% of Patients** | **Epoprostenol Sodium (N=391)** % of patients where event was reported | **Epoprostenol Sodium (N=391)** % of patients where event was dose-limiting |
|---|---|---|
| Flushing | 58 | 14 |
| Headache | 49 | 18 |
| Nausea/Vomiting | 32 | 19 |

| Adverse Events Occurring in ≥ 1% of Patients | Epoprostenol Sodium (N=391) % of patients where event was reported | Epoprostenol Sodium (N=391) % of patients where event was dose-limiting |
|---|---|---|
| Hypotension | 16 | 15 |
| Anxiety, nervousness, agitation | 11 | 7 |
| Chest pain | 11 | 7 |
| Dizziness | 8 | 4 |
| Bradycardia | 5 | 4 |
| Abdominal pain | 5 | 2 |
| Musculoskeletal pain | 3 | 2 |
| Dyspnea | 2 | 2 |
| Back pain | 2 | — |
| Sweating | 1 | ≤ 1 |
| Dyspepsia | 1 | ≤ 1 |
| Hypesthesia/Paresthesia | 1 | ≤ 1 |
| Tachycardia | 1 | ≤ 1 |

**Table 4 : Age-Related Adverse Events During Dose Escalation**

| Adverse Events | < 16 y.o. (N=63) % of patients reporting event | ≥ 16 y.o. (N=328) % of patients reporting event |
|---|---|---|
| Flushing | 14 | 66 |
| Headache | 8 | 57 |
| Nausea/Vomiting | 40 | 30 |
| Hypotension | 14 | 16 |
| Anxiety, nervousness, agitation | 21 | 9 |
| Chest pain | 0 | 13 |
| Dizziness | 2 | 9 |
| Bradycardia | 6 | 5 |
| Abdominal pain | 6 | 5 |

## Adverse Events during Chronic Administration

Interpretation of adverse events is complicated by the clinical features of PAH, which may be 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 jaw pain, flushing, headache, diarrhea, nausea and vomiting, flu-like symptoms, and anxiety/nervousness.

**Adverse Events during Chronic Administration for idiopathic or heritable PAH:** 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 two groups in controlled trials for idiopathic or heritable PAH.

**Table 5 : Adverse Events Regardless of Attribution Occurring in Patients with idiopathic or heritable PAH During Chronic Administration in Controlled Trials with ≥ 10% Difference between Epoprostenol Sodium and Conventional Therapy Alone**

| Adverse Event | Epoprostenol Sodium (N=52) % of patients | Conventional Therapy[a] (N=54) % of patients |
|---|---|---|
| **Occurrence More Common with Epoprostenol Sodium** | | |
| **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 |
| Non-specific 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 Conventional Therapy** | | |
| **Cardiovascular** | | |
| Heart Failure | 31 | 52 |
| Syncope | 13 | 24 |
| Shock | 0 | 13 |
| **Respiratory** | | |
| Hypoxia | 25 | 37 |

[a] Conventional therapy varied among patients and included some or all of the following: anticoagulants, supplemental oxygen, diuretics, oral vasodilators, and digoxin.

Thrombocytopenia, dry mouth, lassitude, chest tightness and bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal) have been reported during uncontrolled clinical trials and post marketing clinical use in patients receiving epoprostenol.

Table 6 lists those additional adverse events reported in patients with idiopathic or heritable PAH receiving epoprostenol plus conventional therapy *versus* conventional therapy alone during controlled clinical trials where the difference in incidence of the event between treatment groups was < 10%.

**Table 6 : Adverse Events Regardless of Attribution Occurring During Chronic Administration in Controlled Trials with < 10% Difference Between Epoprostenol Sodium and Conventional Therapy Alone**

| Adverse Event | Epoprostenol sodium (N=52) % of patients | Conventional Therapy (N=54) % of patients |
|---|---|---|
| **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 |
| 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 |
| 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 |

| Adverse Event | Epoprostenol sodium (N=52) % of patients | Conventional Therapy (N=54) % of patients |
|---|---|---|
| Vision abnormality | 4 | 0 |
| **Other** | | |
| Hemorrhage | 19 | 11 |

Although the number of patients was small, in controlled trials there was a trend towards increased incidence of bradycardia associated with chronic treatment in patients < 16 vs those ≥ 16 years of age. Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of epoprostenol greater than 5 nanograms/kg/min. Bradycardia associated with a considerable fall in systolic and diastolic blood pressure has followed IV administration of a dose of epoprostenol equivalent to 30 nanograms/kg/min in healthy conscious volunteers.

**Adverse Events during Chronic Administration for PAH/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 between the two groups in the controlled trial for patients with PAH/SSD.

**Table 7 : Adverse Events Regardless of Attribution Occurring in Patients with PAH/SSD with ≥ 10% Difference between Epoprostenol Sodium and Conventional Therapy Alone**

| Adverse Event | Epoprostenol Sodium (N=56) % of patients | Conventional Therapy (N=55) % of patients |
|---|---|---|
| **Occurrence More Common with Epoprostenol Sodium** | | |
| **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/Arthralgia | 84 | 65 |
| **Neurological** | | |
| Headache | 46 | 5 |
| **Skin & Appendages** | | |
| Skin ulcer | 39 | 24 |
| Eczema/Rash/Urticaria | 25 | 4 |
| **Occurrence More Common with Conventional Therapy** | | |
| **Cardiovascular** | | |
| Cyanosis | 54 | 80 |
| Pallor | 32 | 53 |

| Adverse Event | Epoprostenol Sodium (N=56) % of patients | Conventional Therapy (N=55) % of patients |
|---|---|---|
| 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 PAH/SSD patients receiving epoprostenol sodium plus conventional therapy or conventional therapy alone during controlled clinical trials.

**Table 8 : Adverse Events Regardless of Attribution Occurring in Patients with PAH/SSD with < 10% Difference between Epoprostenol Sodium and Conventional Therapy Alone**

| Adverse Event* | Epoprostenol Sodium (N=56) % of patients | Conventional Therapy (N=55) % of patients |
|---|---|---|
| **General** | | |
| Asthenia | 100 | 98 |
| Hemorrhage/Hemorrhage injection | 11 | 2 |
| Site/Hemorrhage rectal | | |
| Infection/Rhinitis | 21 | 20 |
| Chills/Fever/Sepsis/Flu-like symptoms | 13 | 11 |
| **Cardiovascular** | | |
| Heart failure/Heart failure right | 11 | 13 |
| Myocardial infarction | 4 | 0 |
| Palpitation | 63 | 71 |
| Shock | 5 | 5 |
| Tachycardia | 43 | 42 |
| Thrombocytopenia | 4 | 0 |
| Vascular disorder peripheral | 96 | 100 |
| Vascular disorder | 95 | 89 |
| **Gastrointestinal** | | |
| Abdominal enlargement | 4 | 0 |
| Abdominal pain | 14 | 7 |
| Constipation | 4 | 2 |
| Flatulence | 5 | 4 |
| **Metabolic** | | |
| Edema/Edema peripheral/Edema genital | 79 | 87 |
| Hypercalcemia | 48 | 51 |
| Hyperkalemia | 4 | 0 |

| Adverse Event* | Epoprostenol Sodium (N=56) % of patients | Conventional Therapy (N=55) % of patients |
|---|---|---|
| Thirst | 0 | 4 |
| **Musculoskeletal** | | |
| Arthritis | 52 | 45 |
| Back pain | 13 | 5 |
| Chest pain | 52 | 45 |
| Cramps leg | 5 | 7 |
| **Respiratory** | | |
| Cough increase | 82 | 82 |
| 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 |
| Sinusitis | 4 | 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 |

* Table lists adverse events which occurred in at least 2 patients in either group

### 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 idiopathic or heritable PAH 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 venous catheter insertion site. During a 12-week controlled trial of PAH/SSD, 14% of patients reported a local infection and 9% of patients reported pain at the venous catheter insertion site. During subsequent long-term follow-up in clinical trials of idiopathic or heritable PAH, sepsis/septicemia (mostly related to delivery system for epoprostenol) was reported at least once in 14% of patients and occurred at a rate of 0.32 infections per patient per year in patients treated with epoprostenol. When suspected, sepsis should be diagnosed and treated quickly. It is therefore important that these patients have immediate access to expert medical care. Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus), reddening over the infusion site and

occlusion of the long IV catheter have been reported. 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, that may lead to serious consequences including death (see WARNINGS, ADVERSE REACTIONS, Adverse Events during Chronic Administration, and OVERDOSAGE).

**Additional Adverse Events**
Very rare cases of splenomegaly and hypersplenism have been observed in the Portopulmonary Hypertension subpopulation of Pulmonary Arterial Hypertension patients treated with epoprostenol.

Very rare cases of ascites associated with long-term epoprostenol use have been observed in Pulmonary Arterial Hypertension patients treated with epoprostenol.

**Post-Marketing Adverse Drug Reactions**
In addition to adverse reactions identified from clinical studies, the following adverse reactions were reported spontaneously to various surveillance systems during post-approval use of epoprostenol.

Endocrine Disorders:
- Hyperthyroidism

Cardiovascular Disorders:
- High output cardiac failure

## OVERDOSAGE

Signs and symptoms of excessive doses of epoprostenol sodium are the expected dose-limiting pharmacologic effects of epoprostenol including flushing, headache, hypotension and complications of hypotension (e.g. tachycardia, nausea, vomiting, and diarrhea). Treatment will ordinarily require dose reduction of epoprostenol or discontinue the infusion and initiate appropriate supportive measures as necessary; for example plasma volume expansion and/or adjustment to pump flow.

One patient with PAH/CTD accidentally received 50 mL of an unspecified concentration of epoprostenol. The patient vomited and became unconscious with an initially unobtainable blood pressure. Epoprostenol was discontinued and the patient regained consciousness within seconds.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

## DOSAGE AND ADMINISTRATION

Epoprostenol for Injection is not to be used for bolus administration. Epoprostenol for Injection

is only indicated for continuous intravenous infusion.

During acute dose-ranging, 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. However, in the rare occurrence of pulmonary edema, chronic treatment is contraindicated.

During chronic use, epoprostenol is delivered continuously on an ambulatory basis through a permanent indwelling central venous catheter. Unless contraindicated, anticoagulant therapy should be administered to patients with idiopathic or heritable PAH receiving epoprostenol 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 epoprostenol as well as in routine catheter care. Because epoprostenol is metabolized rapidly, even brief interruptions in the delivery of epoprostenol may result in symptoms associated with rebound PAH including dyspnea, dizziness, and asthenia. The decision to initiate therapy with epoprostenol should be based upon the understanding that there is a high likelihood that intravenous therapy with epoprostenol will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully considered.

## Dosage

Epoprostenol can be used in acute vasoreactivity studies, to assess pulmonary vasodilator capacity.

### Initial Dosage

Chronic infusion of epoprostenol should be initiated at 2 ng/kg/min and increased until dose-limiting pharmacological effects are elicited or until a tolerance limit to the drug is established and further increases in the infusion rate are not clinically warranted (see Dosage Adjustments). If dose-limiting pharmacologic effects occur, the infusion rate should be decreased to an appropriate chronic infusion rate whereby the pharmacologic effects of epoprostenol 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 per minute is not tolerated, a lower dose which is tolerated by the patient should be identified.

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

### Dosage Adjustments

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

Incremental increases in dose should be considered if symptoms of PAH 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 and tolerability; these intervals should be of at least 15 minutes. 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 pharmacologic events may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dosage decreases should generally be made gradually in 2 ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of epoprostenol or sudden large reductions in infusion rates should be avoided. Except in life-threatening situations (e.g. unconsciousness, collapse, etc.), infusion rates of epoprostenol should be adjusted only under the direction of a physician (see WARNINGS and PRECAUTIONS).

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

**Administration**

**Epoprostenol for Injection (epoprostenol sodium) must be reconstituted only with specific STERILE DILUENT for Epoprostenol for Injection.** Reconstituted solutions of Epoprostenol for Injection must not be diluted or administered with other parenteral solutions or medications (see WARNINGS). Continuous chronic infusion of epoprostenol should be administered through a central venous catheter using an ambulatory infusion pump as recommended by the physician. Temporary peripheral intravenous infusion may be used until central access is established.

The ambulatory infusion pump used to administer Epoprostenol for Injection 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 ±6% of the programmed rate, (5) be positive pressure driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver epoprostenol, and (6) have design characteristics that minimize the likelihood of accidental bolus administration. The reservoir should be made of polyvinyl chloride, or polypropylene, or glass. The infusion pump used in the most recent clinical trials was the CADD-1 HFX 5100 (SIMS Deltec). A 60" microbore non-DEHP extension set with proximal antisyphon valve, low priming volume (0.9 mL), and in-line 0.22 micron filter was used during clinical trials. The final infusion solution must be filtered with a sterile 0.22 micron or 0.20 micron filter prior to, or during administration.

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

Preliminary data suggest that peristaltic pumps may have advantages over syringe pumps.

**Prior to use, reconstituted solutions of Epoprostenol for Injection must be protected from**

**light and must be refrigerated between 2 and 8°C if not used immediately. Under these conditions, reconstituted solution of Epoprostenol for Injection may be stored for up to 40 hours before being transferred to the infusion pump. Reconstituted solution of Epoprostenol for Injection that has been transferred to the infusion pump within 40 hours (i.e. that has not been stored for more than 40 hours) may be used for no longer than 8 hours. Do not freeze reconstituted solutions of Epoprostenol for Injection. Patients should be directed to only use Epoprostenol for Injection with the supplies provided.**

Once placed in the pump, a single reservoir of reconstituted solution of Epoprostenol for Injection can be administered for up to 48 hours by maintaining the temperature between 2 and 8°C with the use of two frozen 6-oz gel packs in a cold pouch. The gel packs should be changed every 12 hours or every 8 hours if the ambient temperature approaches 25°C. **When stored or in use, reconstituted Epoprostenol for Injection must not be exposed to direct sunlight. When administered at room temperature (up to 25°C), the reconstituted solutions may be used for no longer than 12 hours.**

**Reconstitution:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

**Epoprostenol for Injection is only stable when reconstituted with specific STERILE DILUENT for Epoprostenol for Injection. Epoprostenol for Injection must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.**

A concentration for the solution of Epoprostenol for Injection 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. Epoprostenol for Injection, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100 mL. Epoprostenol for Injection should be prepared using 2 vials of the specific STERILE DILUENT for use during a 24-hour period.

Particular care should be taken in the preparation of the infusion and in calculating the rate of infusion. The procedures given below should be closely followed.

**Infusion Rates During Acute Dose Escalation**
Generally, 3000 ng/mL and 10000 ng/mL are satisfactory concentrations to deliver between 2 to 16 ng/kg/min in adults. Infusion rates may be calculated using the following formula:

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

Tables 9 through 12 provide infusion rates for doses up to 16 ng/kg/min based upon patient weight, drug delivery rate, and concentration of the solution of Epoprostenol for Injection to be used. These tables may be used to select the most appropriate concentration of Epoprostenol for Injection that will result in an infusion rate between the minimum and maximum flow rates of the infusion pump and which will allow the desired duration of infusion from a given reservoir

volume.

**Table 9 : Infusion Rates for Epoprostenol for Injection at a Concentration of 3000 ng/mL**

| Dose or Drug Delivery Rate (ng/kg/min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Weight (kg)** | **2** | **4** | **6** | **8** | **10** | **12** | **14** | **16** |
| **Infusion Delivery Rate (mL/hr)** | | | | | | | | |
| **10** | — | — | 1.2 | 1.6 | 2.0 | 2.4 | 2.8 | 3.2 |
| **20** | — | 1.6 | 2.4 | 3.2 | 4.0 | 4.8 | 5.6 | 6.4 |
| **30** | 1.2 | 2.4 | 3.6 | 4.8 | 6.0 | 7.2 | 8.4 | 9.6 |
| **40** | 1.6 | 3.2 | 4.8 | 6.4 | 8.0 | 9.6 | 11.2 | 12.8 |
| **50** | 2.0 | 4.0 | 6.0 | 8.0 | 10.0 | 12.0 | 14.0 | 16.0 |
| **60** | 2.4 | 4.8 | 7.2 | 9.6 | 12.0 | 14.4 | 16.8 | 19.2 |
| **70** | 2.8 | 5.6 | 8.4 | 11.2 | 14.0 | 16.8 | 19.6 | 22.4 |
| **80** | 3.2 | 6.4 | 9.6 | 12.8 | 16.0 | 19.2 | 22.4 | 25.6 |
| **90** | 3.6 | 7.2 | 10.8 | 14.4 | 18.0 | 21.6 | 25.2 | 28.8 |
| **100** | 4.0 | 8.0 | 12.0 | 16.0 | 20.0 | 24.0 | 28.0 | 32.0 |

**Table 10 : Infusion Rates for Epoprostenol for Injection at a Concentration of 5000 ng/mL**

| Dose or Drug Delivery Rate (ng/kg/min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Weight (kg)** | **2** | **4** | **6** | **8** | **10** | **12** | **14** | **16** |
| **Infusion Delivery Rate (mL/hr)** | | | | | | | | |
| **10** | — | — | — | 1.0 | 1.2 | 1.4 | 1.7 | 1.9 |
| **20** | — | 1.0 | 1.4 | 1.9 | 2.4 | 2.9 | 3.4 | 3.8 |
| **30** | — | 1.4 | 2.2 | 2.9 | 3.6 | 4.3 | 5.0 | 5.8 |
| **40** | 1.0 | 1.9 | 2.9 | 3.8 | 4.8 | 5.8 | 6.7 | 7.7 |
| **50** | 1.2 | 2.4 | 3.6 | 4.8 | 6.0 | 7.2 | 8.4 | 9.6 |
| **60** | 1.4 | 2.9 | 4.3 | 5.8 | 7.2 | 8.6 | 10.1 | 11.5 |
| **70** | 1.7 | 3.4 | 5.0 | 6.7 | 8.4 | 10.1 | 11.8 | 13.4 |
| **80** | 1.9 | 3.8 | 5.8 | 7.7 | 9.6 | 11.5 | 13.4 | 15.4 |
| **90** | 2.2 | 4.3 | 6.5 | 8.6 | 10.8 | 13.0 | 15.1 | 17.3 |
| **100** | 2.4 | 4.8 | 7.2 | 9.6 | 12.0 | 14.4 | 16.8 | 19.2 |

**Table 11 : Infusion Rates for Epoprostenol for Injection at a Concentration of 10000 ng/mL**

| Dose or Drug Delivery Rate (ng/kg/min) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient Weight (kg)** | **4** | **6** | **8** | **10** | **12** | **14** | **16** |
| **Infusion Delivery Rate (mL/hr)** | | | | | | | |
| **20** | — | — | 1.0 | 1.2 | 1.4 | 1.7 | 1.9 |
| **30** | — | 1.1 | 1.4 | 1.8 | 2.2 | 2.5 | 2.9 |
| **40** | 1.0 | 1.4 | 1.9 | 2.4 | 2.9 | 3.4 | 3.8 |
| **50** | 1.2 | 1.8 | 2.4 | 3.0 | 3.6 | 4.2 | 4.8 |
| **60** | 1.4 | 2.2 | 2.9 | 3.6 | 4.3 | 5.0 | 5.8 |
| **70** | 1.7 | 2.5 | 3.4 | 4.2 | 5.0 | 5.9 | 6.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **80** | 1.9 | 2.9 | 3.8 | 4.8 | 5.8 | 6.7 | 7.7 |
| **90** | 2.2 | 3.2 | 4.3 | 5.4 | 6.5 | 7.6 | 8.6 |
| **100** | 2.4 | 3.6 | 4.8 | 6.0 | 7.2 | 8.4 | 9.6 |

**Table 12 : Infusion Rates for Epoprostenol for Injection at a Concentration of 15000 ng/mL**

| **Dose or Drug Delivery Rate (ng/kg/min)** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient Weight (kg)** | **4** | **6** | **8** | **10** | **12** | **14** | **16** |
| **Infusion Delivery Rate (mL/hr)** | | | | | | | |
| **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 |

### Infusion Rates during Chronic Infusion

More concentrated solutions than those described in the above tables may be necessary in some cases where higher drug delivery rates are indicated. Generally, over time the daily dose of Epoprostenol for Injection requires up-titration.

## PHARMACEUTICAL INFORMATION

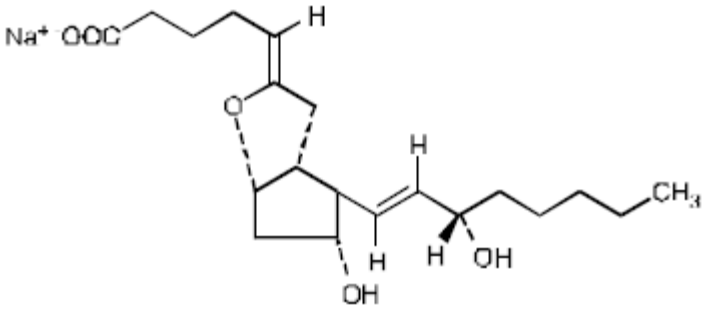
### Drug Substance

Proper Name: Epoprostenol sodium

Chemical Name: [Chem. Abstr.] Prosta-5,13-dien-1-oic acid, 6,9-epoxy-11,15-dihydroxy-, sodium salt (1:1),(5*Z*, 9α, 11α, 13*E*, 15*S*)-

Chemical Name: [IUPAC] Sodium (5*Z*, 13*E*, 15*S*)-6,9α-Epoxy-11α,15-dihydroxyprosta-5,13-dien-1-oate

Structural Formula:




Molecular Formula: $C_{20}H_{31}NaO_5$

Molecular Weight: 374.45 g/mol

Description: Epoprostenol sodium is a white to off-white solid which melts over a range of temperatures from 140 to 170 °C. It is highly soluble in water, methanol and ethanol, and sparingly soluble in aliphatic hydrocarbons.

## COMPOSITION

Epoprostenol for Injection is supplied as a lyophilizate powder for reconstitution for injection.

Each vial of Epoprostenol for Injection contains epoprostenol sodium equivalent to either 0.5 mg epoprostenol or 1.5 mg epoprostenol.

Nonmedicinal ingredients: 50 mg mannitol, 3.76 mg glycine, 2.93 mg sodium chloride, and 2.0 mg sodium hydroxide (to adjust pH).

The STERILE DILUENT is supplied in 50 mL glass vials containing 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (to adjust pH) and water for injection Ph.Eur., q.s. to 50 mL.

LATEX-FREE STOPPER: Stopper contains no dry natural rubber.

## STORAGE AND STABILITY

Store the vials of Epoprostenol for Injection at 15 to 25°C. Protect from light.

Store the vials of STERILE DILUENT for Epoprostenol for Injection at 15 to 25°C.
**Do not freeze.**

**Reconstituted Solutions**
**Epoprostenol for Injection must be reconstituted only with specific STERILE DILUENT for Epoprostenol for Injection.** The reconstituted solution of Epoprostenol for Injection has a pH of 10.3 to 10.8.

The diluent and reconstituted solution should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, the diluent or reconstituted solution should be discarded.

**Preparation:** A concentration for the solution of Epoprostenol for Injection for acute dose-ranging or chronic therapy 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 (see DOSAGE AND ADMINISTRATION, Administration). Epoprostenol for Injection, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100 mL. Epoprostenol for Injection should be prepared using 2 vials of specific STERILE DILUENT for use during a 24-hour period. Table 13 gives directions for preparing several different concentrations of Epoprostenol for Injection.

**Table 13 : Reconstitution and Dilution Instructions**

| Directions | To make 100 mL of Solution with Final Concentration of |
|---|---|
| Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT. Withdraw 3 mL and add to sufficient STERILE DILUENT to make a total of 100 mL. | 3000 ng/mL |
| Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT. Withdraw entire vial contents and add sufficient STERILE DILUENT to make a total of 100 mL. | 5000 ng/mL |
| Dissolve contents of two 0.5 mg vials each with 5 mL of STERILE DILUENT. Withdraw entire vial contents and add sufficient STERILE DILUENT to make a total of 100 mL. | 10000 ng/mL |
| Dissolve contents of one 1.5 mg vial with 5 mL of STERILE DILUENT. Withdraw entire vial contents and add sufficient STERILE DILUENT to make a total of 100 mL. | 15000 ng/mL |

**Prior to use, reconstituted solutions of Epoprostenol for Injection must be protected from light and must be refrigerated between 2 and 8°C if not used immediately. Under these conditions, reconstituted solution of Epoprostenol for Injection may be stored for up to 40 hours before being transferred to the infusion pump. Reconstituted solution of**

**Epoprostenol for Injection that has been transferred to the infusion pump within 40 hours (i.e. that has not been stored for more than 40 hours) may be used for no longer than 8 hours. Do not freeze reconstituted solutions of Epoprostenol for Injection.**

Once placed in the pump, a single reservoir of reconstituted solution of Epoprostenol for Injection can be administered for up to 48 hours by maintaining the temperature between 2 and 8°C with the use of two frozen 6-oz gel packs in a cold pouch. The gel packs should be changed every 12 hours or every 8 hours if the ambient temperature approaches 25°C. **When stored or in use, reconstituted Epoprostenol for Injection must not be exposed to direct sunlight. When administered at room temperature (up to 25°C), the reconstituted solutions may be used for no longer than 12 hours.**

## AVAILABILITY OF DOSAGE FORMS

Epoprostenol for Injection is supplied as a lyophilizate powder for reconstitution in glass vials, box of 1.

- Vial containing epoprostenol sodium equivalent to 0.5 mg epoprostenol
- Vial containing epoprostenol sodium equivalent to 1.5 mg epoprostenol.

The STERILE DILUENT is supplied in 50 mL glass vial closed with rubber stopper and Aluminium / polypropylene cap.

LATEX-FREE STOPPER: Stopper contains no dry natural rubber.

## DETAILED PHARMACOLOGY

**Pharmacodynamics**

**Cardiovascular Pharmacology:** Epoprostenol sodium produces vascular relaxation *in vitro* and systemic, pulmonary, and coronary vasodilation *in vivo* without significant electrocardiographic effects.

In anesthetized rats, epoprostenol sodium (0.125-64 mcg/kg IV) caused dose-dependent decreases in systolic and diastolic blood pressures (up to 100 mmHg) along with tachycardia (up to 66 beats/min) which was reflex in origin. Dose-dependent reductions in mean arterial blood pressure (up to 40 mm Hg) accompanied by tachycardia (up to 80 beats/min) were observed in conscious rats receiving 0.1-1 mcg/kg/min IV.

In anesthetized dogs, epoprostenol sodium (0.01-0.3 mcg/kg/min IV) produced dose-dependent decreases in total peripheral resistance (27-61%), mean arterial blood pressure (15-61%), and pulmonary vascular resistance (32-44%), and increases in cardiac output which were a function of dose-dependent increases in stroke volume (+40% at 0.3 mcg/kg/min).

In conscious dogs, intra-arterial administration of epoprostenol sodium (0.1-1 mcg/kg/min) effected dose-dependent decreases in left ventricular work (-39% at 1 mcg/kg/min) and mean

arterial blood pressure (-28% at 1 mcg/kg/min). Pulmonary artery and renal artery blood flows were increased by 45% and 43% respectively at the highest dose, while most other organs showed dose-dependent decreases in blood flow.

The hypoxia-induced increases in pulmonary arterial blood pressure and pulmonary vascular resistance in anesthetized cats were respectively reduced (by 70%) and abolished by epoprostenol sodium (0.3 mcg/kg/min IV).

The effects of epoprostenol sodium are mediated through a specific membrane receptor, with signal transduction through the adenylate cyclase/cAMP secondary messenger system.

**Neuropharmacological Effects:** Epoprostenol sodium administered as a single intravenous bolus to conscious mice (1-10 mg/kg) and rats (0.1 mcg/kg-100 mg/kg) exerts relatively minor behavioural effects until high doses are achieved. Decreases in body temperature and peripheral flushing are commonly observed secondary to the vasodilation caused by this agent.

**Respiratory Effects:** Epoprostenol sodium has bronchodilator effects in guinea pigs and dogs exposed to the bronchoconstriction induced by histamine, acetylcholine and $PGF_{2\alpha}$.

**Gastrointestinal Effects:** Epoprostenol sodium produces dose-dependent *in vivo* and *in vitro* inhibition of gastric acid secretion induced by histamine and pentagastrin in rats and rat isolated tissue. Dose-dependent inhibition of ethanol-induced gastric lesions in rats has been observed. Gastric emptying may be decreased.

**Endocrine Effects:** The effects of epoprostenol sodium on the circulating levels of anterior pituitary hormones was studied in rats. Although 1 mg/kg epoprostenol sodium given subcutaneously for seven consecutive days was a no-effect dose, 60 mg/kg/day produced decreased plasma leuteinizing hormone but had no effect on follicle stimulating hormone. There were no significant differences in pituitary weights and no drug-related lesions were found by light-microscopy. In a primate luteolysis screening bioassay, 11.5 mg/kg epoprostenol sodium given by intramuscular injection did not produce signs of luteolysis (decreased levels of progesterone).

Subcutaneous injection of 30 mg/kg epoprostenol sodium in two male patas monkeys produced a prominent and persistent increase in plasma cortisol but did not affect either thyroid hormone T3 or T4.

**Renal Effects:** Under basal conditions, epoprostenol sodium causes equivocal changes in urine output and ion excretion. Renal function following ischemia is preserved by treatment with epoprostenol sodium. In rabbits, epoprostenol caused a dose-dependent reduction in glomerular filtration rate.

**Platelet Aggregation:** Epoprostenol sodium is the most potent inhibitor of platelet aggregation known, with profound inhibition of aggregation observed in virtually all species, both *in vivo* and *ex vivo*. Increased bleeding times were observed in rats and dogs.

**Pharmacokinetics**

**Absorption and Disposition:** Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzymatic degradation. In one study in rabbits, after a 107 mg/kg bolus IV dose of $^{3}$H-epoprostenol sodium, clearance was 93 mL/min/kg, volume of distribution was 357 mL/kg, and the terminal half-life was 2.7 min. In a separate study in rabbits, after an 85 mg/kg dose of $^{3}$H-epoprostenol sodium, clearance was 256 mL/min/kg, volume of distribution was 1015 mL/kg, and the terminal half-life was 2.9 min. When rabbits were given intravenous infusions of tritiated epoprostenol sodium (ranging from 4.2 to 604 ng/kg/min), plasma steady-state concentrations were achieved within 15 minutes of initiation of the infusions, and steady-state concentrations increased linearly with increasing infusion rate. A study performed in cats (100 ng/kg/min of $^{3}$H-epoprostenol sodium) using the same analytical methodology, indicated that steady state was achieved by 60 minutes after initiation of the infusion.

**Tissue Distribution:** Tissue distribution studies have been performed in rats given either intravenous or subcutaneous doses of tritiated epoprostenol sodium. Tritium concentrations declined rapidly after either route of administration. The highest levels of radioactivity were observed in the kidney, liver, and small intestine and the lowest levels were observed in brain and adipose tissue. After an IV dose, approximately one-third of the radioactivity was detected in the liver 15 minutes after dosing.

**Elimination and Metabolism:** Epoprostenol undergoes rapid chemical hydrolysis under physiological conditions to yield 6-keto-$PGF_{1\alpha}$. In addition, the metabolism of epoprostenol involves dehydrogenation of the C-15 hydroxyl group, reduction of the 13,14-trans double bond, β-oxidation, ω or ω-1 oxidation. Metabolites consistent with all these metabolic reactions were observed in *in vitro* and *in vivo* studies in rats, dogs and monkeys. In addition, glucuronide-conjugated metabolites have been isolated from rat bile after epoprostenol sodium administration. Cytochrome P-450-dependent epoxidation of epoprostenol has been described *in vitro*. All of the metabolites reported in animal studies are essentially inactive, with the exception of 6-keto-$PGE_1$, that has been detected in dogs but not in any other species. Liver and kidney may be the most important organs with respect to metabolism.

Epoprostenol-derived material is rapidly excreted into urine and feces after dosing with epoprostenol sodium. Dogs excrete nearly 90% of the administered dose in the urine, while in rats there was a more balanced distribution into urine and feces. Monkeys excreted 45.2% of the dose into urine, but fecal recovery was not determined.

## TOXICOLOGY

**Acute Toxicity Studies**

**Rodents:** The acute toxicity of epoprostenol sodium was determined in rodents as follows:

| Strain/Species | No. per Group | Dose (mg/kg) | Route | $LD_{50}$ (mg/kg) |
|---|---|---|---|---|
| **Evans-1 mouse** | 10 M, 10 F | 0, 0.1, 0.3, 1, 10 | IV | > 10 |
| **Evans-1 mouse** | 10 M, 0 F | 0, 0.003, 0.03, 0.1, 0.3, 1 | IV | — |
| **Wistar rat** | 5 M, 5F | 0, 0.0001, 0.01, 1, 100 | IV | 66.3 |

| Strain/Species | No. per Group | Dose (mg/kg) | Route | $LD_{50}$ (mg/kg) |
|---|---|---|---|---|
| | | 25, 35, 50, 70, 80, 100, | | |

The $LD_{50}$ in mice could not be estimated since the maximum dose level of 10 mg/kg epoprostenol was lethal in only 1 of 10 male and in none of 10 female mice.

Epoprostenol 0.0001 mg/kg was without effect. The effects of epoprostenol sodium were observed in mice given doses as low as 0.003 mg/kg. Flaccid paralysis, hypoactivity, ataxia, lost or weak righting reflex, slow and/or deep laboured breathing, ptosis and piloerection were observed following doses of epoprostenol greater than 0.01 mg/kg IV. Signs of toxicity observed 2 to 5 minutes postdose with 0.03 to 10 mg/kg included decreased activity, bradypnea, hypothermia, ataxia, and skin flushing. These signs disappeared in 2 hours postdose. Dose-related hypothermia, which occurred slightly later than the other signs, was most prominent 10 minutes following dosing, but undetectable at 2 hours postdose. With the exception of pulmonary hemorrhage in one male mouse receiving 10 mg/kg, there were no gross lesions in any other animal. Rats given intravenous doses of 100 mg/kg developed respiratory distress, collapsed and died 1 to 10 minutes postdose.

**Subacute and Subchronic Toxicity Studies**

| Strain/Species | No. per Group | Doses | Route | Duration (days) | Drug-Related Findings |
|---|---|---|---|---|---|
| **SD Rat** | 5 M, 5 F | 0, 56, 180, 560 ng/kg/min | Continuous IV | 14 | Weight loss, reddened skin, and decreased platelet counts |
| **Beagle Dog** | 2 M, 2 F | 0, 12.5, 40, 125 ng/kg/min | Continuous IV | 30 | Emesis, soft feces, decreased platelet counts, significantly decreased white blood cells |
| **Beagle Dog** | 2 M, 2 F | 125 ng/kg/min | Continuous IV | 30 | Platelet decreases and hematologic changes reversed |
| **Monkey** *(Erythrocebus patas)* | 2 M, 2 F | 0, 0.01,0.1, 1 mcg/kg/min | IV (1hr/day, 3x /week) | 14 | Emesis, diarrhea, decreased blood pressure, tachycardia, focal necrosis in heart (1 monkey), bleeding time and blood glucose significantly increased |
| **Wistar Rat** | 0 M, 2 F | 0, 1, 10, 30, 60 mg/kg | SC | 7 | Hypotension, EKG changes (myocardial ischemia), necrosis in heart |
| **Wistar Rat** | 15 M, 15 F | 0, 1, 10, 100 mcg/kg | SC | 14 | Red skin, hypotension, EKG changes (myocardial ischemia) |
| **Monkey** *(Erythrocebus patas)* | 1 M, 0 F | Dose escalation 0, 1, 10, 30, 60 mg/kg | SC | 5 | Red skin, hypotension, (all doses), necrosis in heart |

## Carcinogenicity

Carcinogenesis bioassays have not been performed with epoprostenol sodium.

## Mutagenicity

Preliminary studies showed that epoprostenol sodium was non-mutagenic in the Ames Salmonella assay, non-clastogenic in the rat micronucleus assay, and did not damage DNA in the

alkaline elution assay (see below).

| Study | Species | No. per Group | Dose/Concentration | Duration |
|---|---|---|---|---|
| **Ames assay** | *Salmonella typhimurium* | N/A[1] | Up to 2000 mcg/plate | N/A |
| **Micronucleus assay** | Rat | 10 M, 0 F | 0, 10, 20, 40 mg/kg IP | 1 day |
| **Alkaline Elution assay** | *In vitro* | N/A | Up to 3 mM concentration | N/A |

[1] Not applicable

## Reproduction and Teratology

In a Segment I reproduction study in rats, males were treated with 0, 10, 30 or 100 mcg/kg/day subcutaneous epoprostenol sodium for 60 days prior to mating and during a 14-day mating period. Females were treated 14 days before mating and during mating, gestation and lactation. There were no signs of treatment-related effects on fertility of either the parental generation or the first filial generation rats. Estrus cycles of $F_0$ dams were normal. Pregnancies, developmental milestones and behavioural tests were judged to be normal.

There was no teratogenic effect in fetuses from rats and rabbits given epoprostenol sodium by subcutaneous injection during critical periods of organogenesis at dose levels of 1, 10, and 100 mcg/kg/day. Gestation, parturition, and the rearing of young were all normal in rats given subcutaneous doses of 0, 10, 30 and 100 mcg/kg/day.

| Study | Strain/ Species | No. per Group | Route | Dose & Frequency | Drug-Related Findings |
|---|---|---|---|---|---|
| **Segment I Fertility** | SD Rat | 12 M, 24 F | SC | 0, 10, 30, 100 mcg/kg/day 60 days | Depression (all doses), ataxia (30 and 100 mcg/kg); no effect on fertility |
| **Segment II Teratology** | Wistar Rat | 20 F | SC | 0, 1, 10, 100 mcg/kg/day Gestational days 6-16 | No teratogenic effects |
| **Segment III Peri-postnatal** | SD Rat | 24 F | SC | 0, 10, 30, 100 mcg/kg/day Gestational days 15 through Postpartum day 21 | Depression (all doses), ataxia (30 and 100 mcg/kg); slightly delayed parturition; pup survival significantly decreased |
| **Segment II Teratology** | DB Rabbit | 15 F | SC | 0, 1, 10, 100 mcg/kg/day Gestational days 6-18 | No obvious teratogenic effects; technical difficulties with the study |
| **Segment II Teratology** | DB Rabbit | 44 F | SC | 0,100 mcg/kg/day Gestational days 6-18 | Red skin, hypotension; no teratogenic effects |

## Other Toxicity Studies

**Dermal Irritation:** Epoprostenol sodium at a dose of 0.1 mL (1 mg/mL concentration) applied three times in one day to abraded skin of CFLP mice produced no histopathologic alterations.

**Toxicity of Hydrolysis Product:** The subacute toxicity of 6-keto-$PGF_{1\alpha}$ an epoprostenol hydrolysis product, was investigated in patas monkeys. A dose of 1 mcg/kg/min given as a 60-minute intravenous infusion 3 times per week for 2 weeks was devoid of toxic and pharmacodynamic activity.

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## PART III: CONSUMER INFORMATION

### [Pr]Epoprostenol for Injection (epoprostenol sodium)

This leaflet is part III of the "Product Monograph" published when Epoprostenol for Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Epoprostenol for Injection.

**Read all of this leaflet carefully before you start taking this medicine.** Keep this leaflet. You may need to read it again. Contact your doctor, nurse or pharmacist if you have any questions about this medicine.

## ABOUT THIS MEDICATION

**Epoprostenol for Injection is a very complicated medication to administer. The drug must be prepared under rigorous conditions. You will need to learn about the medicine, the delivery system (the central venous catheter) and the pump. You will need to have a 'significant other' who is willing to learn along with you and to be available in case of need. Your doctor or nurse will teach you and your 'significant other' how to prepare the medication and use the pump for administering the medication.**

**What the medication is used for:**
Epoprostenol for Injection is used to treat a lung condition called pulmonary arterial hypertension (PAH). This is where the pressure is high in the main blood vessels in the lungs.

**What it does:**
Epoprostenol for Injection widens the blood vessels to lower the blood pressure in the lungs.

**When it should not be used:**
Do not use Epoprostenol for Injection if you:
- are allergic (hypersensitive) to epoprostenol, the medicinal ingredient in Epoprostenol for Injection, to any other ingredient in the formulation (see "What the nonmedicinal ingredients are" below), or to similar medicines.
- have heart failure.
- had fluid in the lungs (pulmonary edema) when you were started on Epoprostenol for Injection.

If you think any of these apply to you, don't take Epoprostenol for Injection until you have checked with your doctor.

**What the medicinal ingredient is:**
epoprostenol sodium.

**What the nonmedicinal ingredients are:**
The nonmedicinal ingredients in Epoprostenol for Injection and the diluent are glycine, mannitol, sodium chloride, sodium hydroxide, and water for injection.

**What dosage forms it comes in:**
Epoprostenol for Injection comes as a powder in a glass vial. Each vial contains epoprostenol sodium equivalent to either 0.5 mg or 1.5 mg epoprostenol.

Sterile diluent for Epoprostenol for Injection is supplied in 50 mL glass vials.

## WARNINGS AND PRECAUTIONS

BEFORE you use Epoprostenol for Injection talk to your doctor, nurse or pharmacist if you:
- have any problems with bleeding.
- are pregnant, or think you could be, or if you are planning to become pregnant. Your doctor will consider the benefit to you and the risk to your baby of taking Epoprostenol for Injection while you're pregnant.
- are breast-feeding. It is not known whether the ingredients of Epoprostenol for Injection can pass into breast milk.
- are younger than 18 years of age.

BEFORE you use Epoprostenol for Injection, the powder must be dissolved (reconstituted) in the specific liquid (Sterile Diluent) provided.

**Driving and using machines:** Pulmonary arterial hypertension and your treatment may have an effect on your ability to drive or use machinery. Don't drive or use machines unless you're feeling well.

Stopping Epoprostenol for Injection treatment must be done gradually. If the treatment is stopped too quickly, you may get serious side effects, including dizziness, feeling weak and breathing difficulties.

If you have problems with the infusion pump or injection line that stops, or prevents treatment with Epoprostenol for Injection, go to your hospital emergency department immediately.

Infection of the blood (sepsis/septicemia) is a serious common side effect in people taking Epoprostenol for Injection. Symptoms of sepsis include chills, with or without shaking, and fever. If you get any of these symptoms, go to your hospital emergency department immediately.

Avoid situations that can lower blood pressure, including saunas, sunbathing or hot baths.

Your doctor will arrange regular blood tests to check how well your blood clots.

## INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

Some medicines may affect how Epoprostenol for Injection works, or make it more likely that you'll have side effects. Epoprostenol for Injection can also affect how some other medicines work. These include:

- medicines used to prevent blood clots.
- medicines used to dissolve blood clots.
- medicines used for heart failure.
- medicines used for high blood pressure.
- medicines used for angina (chest pain).
- other medicines used to treat pulmonary arterial hypertension.
- medicines to treat inflammation or pain (also called 'NSAIDs').
- digoxin (a medicine used to treat heart disease).
- diuretics (water pill)

## PROPER USE OF THIS MEDICATION

**Usual adult dose:**
Your doctor will decide how much (i.e. dose) and the duration of Epoprostenol for Injection therapy that is right for you. The amount you are given is based on your body weight, and your type of illness. Your dose may be increased or decreased depending on how well you respond to treatment.

Epoprostenol for Injection should only be given by slow continuous infusion (drip) into a vein.

**Overdose:**
Seek urgent medical attention if you think you have used too much Epoprostenol for Injection. Symptoms of overdose may include headache, nausea, vomiting, diarrhea, fast heart rate, warmth or tingling, or feeling like you might pass out (feeling faint/dizziness), unconsciousness, or collapse.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Administration:**
**Initial Treatment**
Your first treatment will be given to you in a hospital. This is because your doctor needs to monitor you and find the best dose for you.

You will start with an infusion of Epoprostenol for Injection. The dose will be increased, until your symptoms are relieved, and any side effects are manageable. Once the best dose has been found, a permanent tube (also referred to as a line or central venous catheter) will be fitted into one of the large veins in your upper chest called a central vein. This is done because Epoprostenol for Injection needs to be given by continuous controlled infusion.

Your doctor will decide which type of catheter is best suited for you. The catheter is a thin soft flexible tube that is inserted under a local anaesthetic in the operating room. Sterile conditions are maintained during this procedure to avoid the risk of infection. You will not feel it inside your body. The catheter has been tunnelled into place inside your chest. The catheter has a Dacron fibre cuff which is under the skin. This will hold the catheter in place and avoid infection. The catheter may also be sutured into position. The tip of the catheter lies in a vein that leads to the entrance of your heart. You can then be treated using an infusion pump that will deliver a prescribed amount of the drug through the catheter directly to your heart.

Your nurse will teach you how to care for the catheter, how to keep the skin around the catheter exit site clean and free from infection. You will learn how to change the dressing and to protect your skin. Your doctor and nurse will make sure that you are comfortable in caring for the catheter exit site. It is very important that you follow all of their instructions carefully (see 'Caring for the Central Venous Catheter' below).

Should you develop sudden fever, contact your doctor as soon as possible.

**Continual Treatment**
Your doctor or nurse will show you how to prepare and use Epoprostenol for Injection and will also advise you how to stop treatment if necessary. Stopping Epoprostenol for Injection must be done gradually. It is very important that you follow all their instructions carefully.

***Steps for Reconstituting Epoprostenol for Injection***
Epoprostenol for Injection comes as a powder in a glass vial. Before use, the powder must be dissolved (reconstituted) in the liquid (Sterile Diluent) provided and used as directed by your doctor. Epoprostenol for Injection should only be used with the supplies provided. Do not use Epoprostenol for Injection if solution shows haziness, particulate matter, discolouration, or leakage. The liquid does not contain a preservative. If you have any of the dose left over, it must be thrown away.

The following instructions explain how to reconstitute Epoprostenol for Injection. **They should supplement the instructions given to you by your doctor or nurse.**

**Epoprostenol for Injection must be reconstituted with specific Sterile Diluent for Epoprostenol for Injection. Reconstituted Epoprostenol for Injection solution should not be mixed with other solutions or medicines prior to or during administration.**

Your doctor will tell you how much Epoprostenol for Injection and Sterile Diluent you will need to use when making up your daily supply. The general procedures for reconstituting Epoprostenol for Injection solution are described below.

1. First, clean your worksite and gather your supplies. Wash your hands thoroughly and then open all the packages. Remove the vial caps from the vial containing specific Sterile Diluent for Epoprostenol for Injection and clean the tops of the vials with alcohol swabs.

2. Once you finish cleaning the tops of your vials and opening your supplies, attach a needle to the syringe. Now break the syringe seal by gently pulling the plunger out slightly and then pushing it back. Draw air into the

syringe; the amount of air that you draw into the syringe should be equal to the amount of Sterile Diluent you've been instructed to withdraw from the vial. Insert the needle through the rubber seal of the vial and press the plunger down to inject the air into the vial. Once all the air has been injected, pull the plunger gently back up to withdraw the prescribed amount of Sterile Diluent. Without withdrawing the needle, invert the vial and syringe and tap the syringe gently so that any air bubbles trapped in the syringe rise towards the top. If necessary, depress the plunger gently to force the air bubbles out and then withdraw sufficient additional Sterile Diluent to restore the required volume in the syringe. Once the required volume has been drawn into the syringe, withdraw the needle.

3. Now insert the needle through the rubber seal of the Epoprostenol for Injection vial and inject the Sterile Diluent gently onto the side of the vial. Always direct the flow of Sterile Diluent towards the side of the vial and inject it gently so that the Epoprostenol for Injection doesn't foam. Allow the pressure to equalize and withdraw the needle from the vial. Now, mix the Epoprostenol for Injection by gently swirling the vial. Turn the vial upside down to catch any undissolved powder near the top. **Never shake the vials.** If you need to mix more than one vial of Epoprostenol for Injection, simply repeat this process.

4. Your doctor or nurse will advise you on the amount of reconstituted Epoprostenol for Injection to be withdrawn. First, by gently pulling the plunger back, fill the syringe with the amount of air that is equal to the amount of Epoprostenol for Injection to be withdrawn. Remember to wipe the tops of the vials with an alcohol swab. Now, insert the needle through the seal of the Epoprostenol for Injection vial and inject the air. Then pull the plunger gently back to withdraw the reconstituted Epoprostenol for Injection into the syringe. Remove any air that may be trapped in the syringe as described in step 2 above. Withdraw the needle and place the cap back on the syringe.

5. You are now ready to inject the Epoprostenol for Injection into your cassette. Remove the end cap from the cassette tubing; then carefully remove the needle from the syringe, discard in an appropriate manner and attach the syringe to the cassette tubing. Now, while holding the cassette in one hand, you can use the tabletop as a third hand while you push down on the syringe to inject the solution into the cassette. Once the syringe is empty, clamp the cassette tubing near the syringe, disconnect the syringe and cap the tubing with the red cap.

6. Now you will withdraw the contents of the Sterile Diluent vials and inject them into the cassette. Using a 60 cc syringe, attach a new needle to the syringe, break the seal on the syringe by pulling the plunger out and pushing it back in. Next, fill the syringe with the amount of air that is equal to the amount of Sterile Diluent you will remove from the first vial. Remember to wipe the top of the Sterile Diluent vial with an alcohol swab before you insert the needle. Once it is dry, insert the needle through the rubber seal, inject some of the air into the vial and allow the fluid to flow into the syringe. With the larger syringe, it may be easier to hold it in the vertical position. Push more air in as needed until you have withdrawn all of the contents of the vial. Remove any air that may be in the syringe as described in step 2 above. Once the vial is emptied, allow the pressure to equalize before you pull the needle out. If you don't, you may lose fluid from the syringe or the vial and you would need to start the whole process over again. Withdraw the needle and place the cap back on the syringe.

7. Now you are ready to inject the first syringe full of Sterile Diluent into the cassette. To do this, first uncap the cassette tubing. Then carefully remove the needle from the syringe, discard in an appropriate manner and attach the syringe to the cassette tubing. Unclamp the cassette tubing and then carefully inject the solution into the cassette. When the syringe is empty, clamp the cassette tubing near the syringe, disconnect the syringe and cap the cassette tubing. You will repeat this same process to transfer the contents of the required Sterile Diluent vial as specified by your doctor or nurse into the cassette.

8. After you have completed the transfer of all the required Sterile Diluent, leave the syringe attached to the cassette tubing while you mix the solution. Gently invert the cassette at least 10 times, thoroughly mixing the Epoprostenol for Injection. Now you need to remove all the air from the cassette.

9. In order to remove the air inside the cassette, first you have to collect the air bubbles. Simply rotate the cassette around until all of the small bubbles join to form one big air pocket. Then tilt the cassette carefully so that the air pocket is in the corner where the tubing connects to the bag. To remove the air from the cassette, unclamp the tubing and pull back the plunger of the syringe until you see fluid fill the tubing. Then clamp the tubing near the connector, disconnect it and cap it with the red cap. To avoid any confusion, label the cassette with the date and time you made up the Epoprostenol for Injection.

Now put the cassette into the refrigerator until it is time to use it. Store it on the top shelf to avoid spilling any food or drink onto your cassette. Always have a back-up cassette that is ready for use.

***Steps for Administering Epoprostenol for Injection for Injection by a Continuous Infusion Pump***

You will use a pump to receive medication by continuous delivery. The instructions for use may vary depending on the particular make and model of the pump you are using. To avoid any potential interruptions in Epoprostenol for Injection delivery, you should have access to a back-up infusion pump and intravenous infusion sets.

Your doctor or nurse will give detailed instructions on how to use and care for the specific pump and accessories that you will use for administering the medicine (including changing the pump battery, cassette and tubing).

The temperature of the Epoprostenol for Injection solution inside the pump can be maintained for up to 48 hours at 2° to 8 °C with the use of a 'cold pouch' containing two frozen 6-oz gel packs. **Remember to change the gel packs every 12 hours or every 8 hours if room temperature approaches 25 °C. When stored or in use, Epoprostenol for Injection must not be exposed to light.**

***Steps for Caring for the Central Venous Catheter***
Change the dressing on the catheter exit site 1 to 2 times per week or more frequently if needed.

You will need the following equipment: dressing set, 2 sterile containers, povidone-iodine antiseptic solution, gauze swabs, 70% alcohol, povidone-iodine antiseptic ointment, sterile cotton swabs, adhesive tape (non-allergenic), transparent dressing 10 cm x 12 cm or 6 cm x 7 cm.

**Maintain sterile technique at all times. If you suspect that you have contaminated anything, discard the equipment and begin again.**

1. Assemble equipment.
2. Stabilize catheter while removing old transparent dressing.
3. Open sterile dressing kit.
4. Pour alcohol into sterile container.
5. Pour povidone-iodine antiseptic solution into sterile container.
6. Squeeze povidone-iodine antiseptic ointment onto sterile field.
7. Open transparent dressings onto sterile field.
8. Remove old transparent dressing.
9. Clean the catheter exit site with povidone-iodine antiseptic solution soaked 2" x 2" gauze swabs, starting at the catheter exit site. Work outward in a circular extending motion extending to an 8 cm radius.
10. Repeat step 9 three times.
11. **Never return to the catheter exit site using the same swab.**
12. Repeat steps 9 and 10 using an alcohol soaked 2" x 2" gauze swab.
13. Apply povidone-iodine antiseptic ointment to the catheter exit site with a sterile cotton swab.
14. Apply new sterile transparent dressing.
15. Tape catheter to skin using 'stress loop'.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- headache
- jaw pain
- diarrhea, nausea, vomiting
- stomach discomfort or pain, dry mouth
- pain (chest, bone, muscle and/or joint)
- feeling anxious, nervous, and/or agitated
- rash
- pain and/or redness at the injection site
- sweating, redness of your face (flushing)
- feeling tired, weak
- pale skin

If any of these affects you severely, tell your doctor, nurse or pharmacist.

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your doctor, nurse or pharmacist | | Seek immediate medical help |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Common | **Bleeding and decreased platelets:** bleeding that lasts longer than usual or which cannot be stopped, bruising more easily than normal. fatigue and weakness. | | ✓ | |
| Common | **Low blood pressure or unusually fast or slow heart beat:** dizziness, fainting, lightheadedness may occur when you go from lying or sitting to standing up. | ✓ | | |
| Common | **Blood infection (sepsis/septicemia):** chills, with or without shaking, and fever. | | | ✓ |
| Uncommon | **Build up of fluid in the lungs (pulmonary edema):** swelling or difficulty breathing. | | | ✓ |
| Rare | **Injection site infection:** redness, tenderness, swelling or pus at infusion site. | | | ✓ |
| Very Rare | **Ascites:** swelling due to build up of fluid around the stomach | | ✓ | |
| Very Rare | **Hyperthyroid (overactive thyroid):** weight loss, fast heartbeat, sweating, frequent bowel movements, thin brittle hair and/or skin, sweating, anxiety, nervousness. | | ✓ | |
| Very Rare | **Enlarged spleen:** upper left abdominal discomfort, fullness or pain, problems digesting a large meal. | | ✓ | |
| Very Rare | **Injection site reaction:** tenderness, burning, stinging, swelling, redness, blistering or peeling. | | | ✓ |
| Very Rare | **Injection line blockage:** dizziness, weakness and breathing difficulties. | | | ✓ |

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | Talk with your doctor, nurse or pharmacist | | Seek immediate medical help |
|---|---|---|---|
| | Only if severe | In all cases | |
| Heart attack: Feeling of tightness around the chest; pain radiating into the arm or jaw combined with shortness of breath, nausea and lightheadedness. | | | ✓ |
| Too much pumping of blood from the heart (high cardiac output failure): Leading to persistent cough, shortness of breath, fatigue, swelling of the legs and abdomen due to fluid build-up | | ✓ | |

***This is not a complete list of side effects. For any unexpected effects while taking Epoprostenol for Injection, contact your doctor or pharmacist.***

## HOW TO STORE IT

Keep out of the reach and sight of children.

Do not use Epoprostenol for Injection after the expiry date on the label.

Store the vials of Epoprostenol for Injection at 15° to 25 °C. Protect from light by keeping Epoprostenol for Injection in its carton until it is used.

Store the vials of STERILE DILUENT for Epoprostenol for Injection at 15° to 25° C. **Do not freeze**.

**Reconstituted Solution**

Prior to use, reconstituted solutions of Epoprostenol for Injection must be protected from light and must be refrigerated at 2° to 8° C if not used immediately. Under these conditions, reconstituted Epoprostenol for Injection may be stored for up to 40 hours before being transferred to the infusion pump. Reconstituted Epoprostenol for Injection solution that has been transferred to the infusion pump within 40 hours (i.e. that has not been stored for more that 40 hours) may be used for no longer than 8 hours. **Do not freeze** reconstituted solutions of Epoprostenol for Injection. **When stored or in use, reconstituted Epoprostenol for Injection must not be exposed to direct sunlight. When administered at room temperature (up to 25°C), the reconstituted solutions may be used for no longer than 12 hours.**

## REPORTING SUSPECTED SIDE EFFECTS

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    **Health Canada**
    **Postal Locator 0701E**
    **Ottawa, Ontario**
    **K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Sandoz Canada Inc., at:

1-800-361-3062

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110 rue de Lauzon
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medinfo@sandoz.com

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