EPOPROSTENOL SODIUM- epoprostenol sodium injection, powder, for solution
STERILE DILUENT- sterile diluent injection
Teva Parenteral Medicines, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPOPROSTENOL SODIUM FOR INJECTION safely and effectively. See full prescribing information for EPOPROSTENOL SODIUM FOR INJECTION.

EPOPROSTENOL SODIUM for injection, for intravenous use

Initial U.S. Approval: 1995

INDICATIONS AND USAGE

Epoprostenol sodium for injection is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly (97%) patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%). (1)

DOSAGE AND ADMINISTRATION

- Initiate intravenous infusion through a central venous catheter at 2 ng/kg/min. (2.2, 2.3)
- Change dose in 1-to 2-ng/kg/min increments at intervals of at least 15 minutes based on clinical response. (2.2)
- Avoid sudden large dose reductions. (2.2, 5.2)

DOSAGE FORMS AND STRENGTHS

For injection: 0.5 mg or 1.5 mg of epoprostenol freeze-dried powder in a single-dose vial for reconstitution with the supplied diluent. (3)

CONTRAINDICATIONS

- Heart failure with reduced ejection fraction. (4)
- Hypersensitivity to epoprostenol or any of its ingredients. (4)

WARNINGS AND PRECAUTIONS

- Pulmonary edema: Discontinue therapy if pulmonary edema occurs. (5.1)
- Rebound pulmonary hypertension: Do not abruptly discontinue or decrease the dose. (5.2)
- Vasodilation reactions: Monitor blood pressure and symptoms regularly during initiation and after dose change. (5.3)
- Increased risk for bleeding: Increased risk for hemorrhagic complications, particularly for patients with other risk factors for bleeding. (5.4)

ADVERSE REACTIONS

The most common adverse reactions are dizziness, jaw pain, headache, musculoskeletal pain, and nausea/vomiting, and are generally associated with vasodilation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2019

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Epoprostenol Sodium for Injection 0.5 mg/vial, Carton Text
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Epoprostenol sodium for injection is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise capacity. Trials establishing effectiveness included predominantly (97%) patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).

2 DOSAGE AND ADMINISTRATION

2.1 Reconstitution

Each vial is for single dose only; discard any unused diluent or unused reconstituted solution.

Select a concentration for the solution of epoprostenol sodium for injection 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 below *[see Dosage and Administration (2.4)]*.

Using aseptic technique, reconstitute epoprostenol sodium for injection only with STERILE DILUENT for epoprostenol sodium for injection. Table 1 gives directions for preparing several different concentrations of epoprostenol sodium for injection. See Table 2 for storage and administration time limits for the reconstituted epoprostenol sodium for injection.

Table 1. Reconstitution and Dilution Instructions for Epoprostenol Sodium for Injection Using STERILE DILUENT for Epoprostenol Sodium for Injection.

To make 100 mL of solution with final concentration of:	Directions:
3,000 ng/mL	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.
5,000 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.
10,000 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.
15,000 ng/mL[a]	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.
[a] Higher concentrations may be prepared for patients who receive epoprostenol sodium for injection long-term.	

Table 2. Storage and Administration Limits for Reconstituted Epoprostenol Sodium for Injection

	When Using STERILE DILUENT for Epoprostenol Sodium for Injection
Stability	When used at room temperature, (15°C to 25°C; 59°F to 77°F) reconstituted solutions: • are stable for up to 8 hours following reconstitution or removal from refrigerated storage. • may be stored for up to 40 hours refrigerated at 2°C to 8°C (36°F to 46°F) before use. When used with a cold pack, reconstituted solutions: • are stable for up to 24 hours use. • may be stored refrigerated at 2°C to 8°C (36°F to 46°F) before use as long as the total time of refrigerated storage and infusion does not exceed 48 hours. • Change cold packs every 12 hours.
• Reconstituted solutions can be used immediately. Refrigerate at 2°C to 8°C (36°F to 46°F) if not used immediately. • Protect from light. • Do not freeze reconstituted solutions.	

2.2 Dosage

Initiate intravenous infusions of epoprostenol sodium for injection at 2 ng/kg/min. Alter the infusion 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.

During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output may occur. In such cases, consider dose reduction, but such an increase does not imply that chronic treatment is contraindicated.

Base changes in the chronic infusion rate on persistence, recurrence, or worsening of the patient's

symptoms of pulmonary hypertension and the occurrence of adverse vasodilatory reactions. In general, expect progressive increases in dose.

If dose-related adverse reactions occur, make dose decreases gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve *[see Adverse Reactions (6.1, 6.2)]*. Avoid abrupt withdrawal of epoprostenol sodium for injection or sudden large reductions in infusion rates *[see Warnings and Precautions (5.2)]*.

Following establishment of a new chronic infusion rate, measure standing and supine blood pressure for several hours.

Taper doses of epoprostenol sodium for injection after initiation of cardiopulmonary bypass in patients receiving lung transplants.

2.3 Administration

Initiate epoprostenol in a setting with adequate personnel and equipment for physiologic monitoring and emergency care.

Inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, do not use.

Administer continuous chronic infusion of epoprostenol sodium for injection through a central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Do not administer bolus injections of epoprostenol sodium for injection.

The ambulatory infusion pump used to administer epoprostenol sodium 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, and (5) be positive-pressure-driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver epoprostenol sodium for injection. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. Use a 60-inch microbore non-di-(2-ethylhexyl)phthalate (DEHP) extension set with proximal antisyphon valve, low-priming volume (0.9 mL), and in-line 0.22-micron filter.

To avoid interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets.

Do not administer or dilute reconstituted solutions of epoprostenol sodium for injection with other parenteral solutions or medications. Consider a multi-lumen catheter if other intravenous therapies are routinely administered.

Select a concentration for the solution of epoprostenol sodium for injection 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. When administered chronically, prepare epoprostenol sodium for injection in a drug delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100 mL, using 2 vials of STERILE DILUENT for epoprostenol sodium for injection.

Generally, 3,000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between 2 to 16 ng/kg/min in adults. Higher infusion rates, and therefore, more concentrated solutions, may be necessary with long-term administration of epoprostenol sodium for injection.

Infusion rates may be calculated using the following formula:

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

Example calculations for infusion rates are as follows:

Example 1: for a 60-kg person at the recommended initial dose of 2 ng/kg/min using a 3,000-ng/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate} \text{ (mL/h)} = \frac{\textbf{[2} \text{ (ng/kg/min)} \times \textbf{60} \text{ (kg)} \times \textbf{60 (}\text{min/h)}\textbf{]}}{} = \textbf{2.4} \text{ (mL/h)}$$

3,000 (ng/mL)

Example 2: for a 70-kg person at a dose of 16 ng/kg/min using a 15,000-ng/mL concentration, the infusion rate would be as follows:

Infusion Rate (mL/h) = **[16** (ng/kg/min) × **70** (kg) × **60 (**min/h)**]** = **4.48** (mL/h)
15,000 (ng/mL)

3 DOSAGE FORMS AND STRENGTHS

For injection: 0.5 mg or 1.5 mg of epoprostenol, freeze-dried powder in a single-dose vial for reconstitution with the supplied diluent.

4 CONTRAINDICATIONS

Epoprostenol is contraindicated in patients with heart failure caused by reduced left ventricular ejection fraction *[see Clinical Studies (14.3)]*.

Epoprostenol is contraindicated in patients with a hypersensitivity to the drug or any of its ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Edema

If the patient develops pulmonary edema during initiation with epoprostenol, discontinue therapy and do not readminister. Consider the possibility of associated pulmonary veno-occlusive disease in such patients.

5.2 Rebound Pulmonary Hypertension following Abrupt Withdrawal

Avoid abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in dosage of epoprostenol because symptoms associated with rebound pulmonary hypertension (e.g., dyspnea, dizziness, and asthenia) may occur. In clinical trials, one Class III patient's death was judged attributable to the interruption of epoprostenol.

5.3 Vasodilation

Epoprostenol is a potent pulmonary and systemic vasodilator and can cause hypotension and other reactions such as flushing, nausea, vomiting, dizziness, and headache. Monitor blood pressure and symptoms regularly during initiation and after dose change *[see Dosage and Administration (2.2)]*.

5.4 Increased Risk for Bleeding

Epoprostenol is a potent inhibitor of platelet aggregation. Therefore, expect an increased risk for hemorrhagic complications, particularly for patients with other risk factors for bleeding *[see Clinical Pharmacology (12.3)]*.

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions are shown in Table 3 and are generally related to vasodilatory effects.

Table 3. Adverse Reactions Occurring in Patients with Idiopathic or Heritable PAH and with PAH Associated with Scleroderma Spectrum of Diseases (PAH/SSD) Occurring ≥10% More

Frequently on Epoprostenol than Conventional Therapy

Adverse Reaction	Idiopathic or Heritable PAH		PAH/SSD	
	Epoprostenol (n = 52)	Conventional Therapy (n = 54)	Epoprostenol (n = 56)	Conventional Therapy (n = 55)
Body as a whole				
Jaw pain	54%	0%	75%	0%
Nonspecific musculoskeletal pain	35%	15%	84%	65%
Headache	83%	33%	46%	5%
Chills/fever/sepsis/flu-like symptoms	25%	11%	13%	11%
Cardiovascular system				
Flushing	42%	2%	23%	0%
Hypotension	27%	31%	13%	0%
Tachycardia	35%	24%	43%	42%
Digestive system				
Anorexia	25%	30%	66%	47%
Nausea/Vomiting	67%	48%	41%	16%
Diarrhea	37%	6%	50%	5%
Skin and Appendages				
Skin ulcer	-	-	39%	24%
Eczema/rash/urticaria	10%	13%	25%	4%
Musculoskeletal system				
Myalgia	44%	31%	-	-
Nervous system				
Anxiety/hyperkinesias/nervousness /tremor	21%	9%	7%	5%
Hyperesthesia/hypesthesia/paresthesia	12%	2%	5%	0%
Dizziness	83%	70%	59%	76%

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 PAH trials of up to 12 weeks' duration, the local infection rate was about 18% and the rate for pain was about 11%. During long-term follow-up, sepsis was reported at a rate of 0.3 infections/patient per year in patients treated with epoprostenol.

6.2 Postmarketing Experience

The following events have been identified during postapproval use of epoprostenol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic

Anemia, hypersplenism, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac

High output cardiac failure.

Endocrine and Metabolic

Hyperthyroidism.

Gastrointestinal

Hepatic failure.

Respiratory, Thoracic, and Mediastinal

Pulmonary embolism.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited published data from case series and case reports have not established an association with epoprostenol and major birth defects, miscarriage or adverse maternal or fetal outcomes when epoprostenol is used during pregnancy. There are risks to the mother and fetus from untreated pulmonary arterial hypertension *(see Clinical Considerations)*. In animal reproduction studies, pregnant rats and rabbits received epoprostenol sodium during organogenesis at exposures of 2.5 and 4.8 times the maximum recommended human dose (MRHD), respectively, and there was no effect on the fetus (*see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women with untreated pulmonary arterial hypertension are at risk for heart failure, stroke, preterm delivery, and maternal and fetal death.

Data

Animal Data: Embryo-fetal development studies have been performed in rats and rabbits during organogenesis. Epoprostenol sodium doses up to 100 mcg/kg/day, a dose that was maternally toxic in rabbits but not in rats, (600 mcg/m^2/day in rats, 2.5 times the MRHD, and 1,180 mcg/m^2/day in rabbits, 4.8 times the MRHD based on body surface area), had no effect on the fetus.

In a postnatal development study, epoprostenol sodium was administered subcutaneously to female rats for 2 weeks prior to mating through weaning and to male rats for 60 days prior to and through mating at a male and female toxic dose of up to 100 mcg/kg/day (600 mcg/m^2/day, 2.5 times the MRHD based on body surface area). There was no effect on growth and development of the offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of epoprostenol in either human or animal milk, the effects on the breastfed infant, or the effect on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for epoprostenol and any potential adverse effects on the breastfed child from epoprostenol or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials of epoprostenol in pulmonary hypertension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. 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

Hypoxemia, hypotension, and respiratory arrest leading to death have been reported in clinical practice following overdosage of epoprostenol.

Excessive doses of epoprostenol were associated with flushing, headache, hypotension, tachycardia, nausea, vomiting, and diarrhea during clinical trials.

One patient with PAH/SSD 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.

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.

Treatment

Discontinue or reduce dose of epoprostenol.

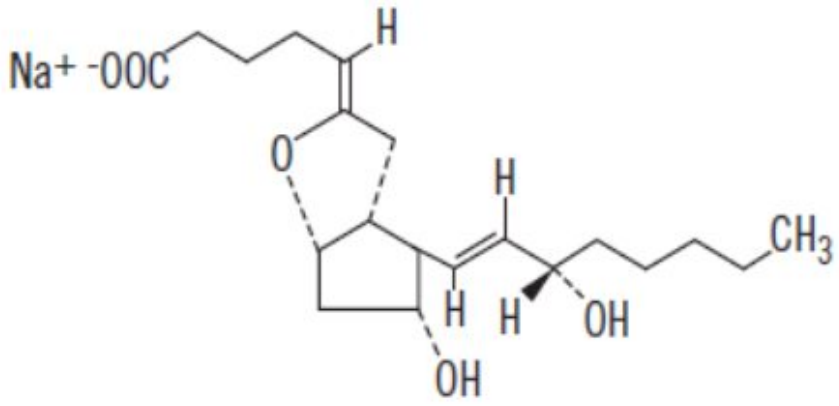
11 DESCRIPTION

Epoprostenol sodium for injection is a sterile sodium salt formulated for intravenous (IV) administration. Each vial of epoprostenol sodium for injection contains epoprostenol sodium equivalent to either 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 3.76 mg glycine, 50 mg mannitol, and 2.93 mg sodium chloride. Sodium hydroxide may have been added to adjust pH.

Epoprostenol (PGI_2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

Epoprostenol is (5Z,9α,11α,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 $C_{20}H_{31}NaO_5$. The structural formula is:



Epoprostenol sodium for injection is a white to off-white powder that must be reconstituted with STERILE DILUENT for epoprostenol sodium for injection. STERILE DILUENT for epoprostenol sodium for injection is supplied in glass vials containing 50 mL of 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (added to adjust pH), and Water for Injection, USP.

The reconstituted solution of epoprostenol sodium for injection has a pH of 11.0 to 11.8 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

Acute Hemodynamic Effects

Acute intravenous infusions of epoprostenol for up to 15 minutes in patients with idiopathic or heritable PAH or PAH/SSD 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 artery pressure (PAPm) were variable and minor.

In humans, hemodynamic changes due to epoprostenol (e.g., increased heart rate, facial flushing) returned to baseline within 10 minutes of termination of 60-minute infusions of 1 to 16 ng/kg/min. This pharmacodynamic behavior is consistent with a short in vivo half-life and rapid clearance in humans, as suggested by the results of animal and in vitro studies.

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.

Drug Interaction Studies

Additional reductions in blood pressure may occur when epoprostenol is administered with diuretics, antihypertensive agents, or other vasodilators.

When other antiplatelet agents or anticoagulants are used concomitantly, there is a potential for epoprostenol to increase the risk of bleeding. However, patients receiving infusions of epoprostenol in clinical trials were maintained on anticoagulants without evidence of increased bleeding.

12.3 Pharmacokinetics

Absorption/Distribution

Epoprostenol is rapidly hydrolyzed at neutral pH in blood 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-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.

Metabolism

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-$PGF_{1\alpha}$ (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-$PGF_{1\alpha}$ (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.

Elimination

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.

Drug Interaction Studies

In a pharmacokinetic substudy in patients with congestive heart failure receiving furosemide in whom

therapy with epoprostenol was initiated, apparent oral clearance values for furosemide (n = 23) were decreased by 13% 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.

In a pharmacokinetic substudy in patients with congestive heart failure receiving digoxin in whom therapy with epoprostenol was initiated, apparent oral clearance values for digoxin (n = 30) were decreased by 15% on the second day of therapy and returned to baseline values by Day 87. Clinical significance of this interaction is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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.

In a fertility/postnatal development study, epoprostenol sodium was administered subcutaneously to female rats for 2 weeks prior to mating through weaning and to male rats for 60 days prior to and through mating at an adult toxic dose of up to 100 mcg/kg/day (600 mcg/m^2/day, 2.5 times the MRHD based on body surface area). There was no effect on fertility in female or male rats.

14 CLINICAL STUDIES

14.1 Chronic Infusion in Idiopathic or Heritable PAH

Hemodynamic Effects

Chronic continuous infusions of epoprostenol in patients with idiopathic or heritable PAH were studied in 2 prospective, open, randomized trials of 8 and 12 weeks' duration comparing epoprostenol plus conventional therapy with conventional therapy alone. Dosage of epoprostenol was determined as described in *Dosage and Administration (2)* and averaged 9.2 ng/kg/min at trials' 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 NYHA Functional Class II patients, all patients were either functional Class III or Class IV. As results were similar in the 2 trials, 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 with those who did not. Table 4 illustrates the treatment-related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

Table 4. Hemodynamics during Chronic Administration of Epoprostenol in Patients with Idiopathic or Heritable PAH

Hemodynamic Parameter	Baseline		Mean Change from Baseline at End of Treatment Period[a]	
	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[b]	-0.1
PAPm (mm Hg)	60	60	-5[b]	1

PVR (Wood U)	16	17	-4[b]	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6[b]	-1
TPR (Wood U)	20	21	-5[b]	1

[a] 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).
[b] Denotes statistically significant difference between group receiving epoprostenol and group receiving conventional therapy.
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 trial.

The acute hemodynamic response to epoprostenol did not correlate well with improvement in exercise tolerance or survival during chronic use of epoprostenol.

Clinical Effects

A 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 with 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, respectively.

Survival was improved in 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 trial. 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 ($P = 0.003$).

14.2 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 (n = 56) with conventional therapy alone (n = 55). Except for 5 NYHA Functional Class II patients, all patients were either functional Class III or Class IV. 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 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.

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 with those who did not. Table 5 illustrates the treatment-related hemodynamic changes in these patients after 12 weeks of treatment.

Table 5. Hemodynamics during Chronic Administration of Epoprostenol in Patients with PAH/SSD

		Mean Change from Baseline at 12 Weeks

Hemodynamic Parameter	Baseline			
	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[a]	-0.1
PAPm (mm Hg)	51	49	-5[a]	1
RAPm (mm Hg)	13	11	-1[a]	1
PVR (Wood U)	14	11	-5[a]	1
SAPm (mm Hg)	93	89	-8[a]	-1

[a] Denotes statistically significant difference between group receiving epoprostenol and group receiving conventional therapy (n is the number of patients with hemodynamic data).
CI = Cardiac index, PAPm = Mean pulmonary arterial pressure, RAPm = Mean right arterial 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 with 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 with 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.

No statistical difference in survival over 12 weeks was observed in patients with PAH/SSD treated with epoprostenol as compared with 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.

14.3 Increased Mortality in Patients with Heart Failure Caused by Severe Left Ventricular Systolic Dysfunction

A large trial 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 epoprostenol in patients with heart failure due to severe left ventricular systolic dysfunction is therefore contraindicated.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Epoprostenol sodium for injection is supplied as a sterile freeze-dried powder in 10 mL flint glass vials with gray butyl rubber closures, individually packaged in a carton.

NDC 0703-**1985**-01	10 mL vial containing epoprostenol sodium equivalent to 0.5 mg (500,000 ng), carton of 1.
NDC 0703-**1995**-	10 mL vial containing epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng),

01	carton of 1.

The STERILE DILUENT for Epoprostenol Sodium for Injection is supplied in flint glass vials containing 50 mL diluent with butyl rubber closures.

NDC 0703-**9258**-09 50 mL of STERILE DILUENT for Epoprostenol Sodium for Injection, tray of 2 vials.

16.2 Storage and Handling

Proper storage and handling are essential to maintain the potency of epoprostenol sodium for injection.

Unopened vials of epoprostenol sodium for injection powder are stable until the date indicated on the package when stored at room temperature, 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] and protected from light in the carton.

Unopened vial of STERILE DILUENT for epoprostenol sodium for injection is stable until the date indicated on the package when stored at room temperature, 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. DO NOT FREEZE.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients:

- Epoprostenol sodium for injection must be reconstituted only with STERILE DILUENT for epoprostenol sodium for injection.
- Reconstituted solution prepared with STERILE DILUENT for epoprostenol sodium for injection must be used with a cold pouch if not administered within 8 hours.
- Epoprostenol sodium for injection is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with epoprostenol sodium for injection requires commitment by the patient to drug reconstitution, drug administration, and care of the permanent central venous catheter. Patients must adhere to sterile technique in preparing the drug and in the care of the catheter, and even brief interruptions in the delivery of epoprostenol sodium for injection may result in rapid symptomatic deterioration. A patient's decision to receive epoprostenol sodium for injection should be based upon the understanding that there is a high likelihood that therapy with epoprostenol sodium for injection will be needed for prolonged periods, possibly years. Consider the patient's ability to accept and care for a permanent intravenous catheter and infusion pump.
- To adjust infusion rates of epoprostenol sodium for injection only under the direction of a physician.
- To avoid interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets.
- To contact their healthcare providers if any unusual bruising or bleeding develops.

Teva Pharmaceuticals USA, Inc.

North Wales, PA 19454

Rev. E 3/2019

PATIENT INFORMATION

Epoprostenol Sodium (e" poe pros' te nol soe' dee um) for Injection, for intravenous use
What is epoprostenol sodium for injection? Epoprostenol sodium for injection is a prescription medicine used to treat people with certain types of pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of the lungs. Epoprostenol

sodium for injection can improve your ability to be physically active.
It is not known if epoprostenol sodium for injection is safe and effective in children.

Do not use epoprostenol sodium for injection if you:

- have certain types of heart failure. Talk to your healthcare provider before using epoprostenol sodium for injection if you have heart failure.
- are allergic to epoprostenol sodium for injection or any of the ingredients in epoprostenol sodium for injection. See the end of this leaflet for a complete list of ingredients in epoprostenol sodium for injection.

Before you use epoprostenol sodium for injection, tell your healthcare provider about all of your medical conditions, including if you:

- are allergic to any medicine.
- are pregnant or plan to become pregnant. It is not known if epoprostenol sodium for injection will harm your unborn baby. You and your healthcare provider should decide if you will use epoprostenol sodium for injection.
- are breastfeeding or plan to breastfeed. It is not known if epoprostenol sodium for injection passes into your breast milk. You and your healthcare provider should decide if you will take epoprostenol sodium for injection or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you take:

- a “water pill” (diuretic)
- a medicine for high blood pressure (hypertension)
- a blood thinner medicine (antiplatelet or anticoagulant medicine)

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.
Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I use epoprostenol sodium for injection?

- Epoprostenol sodium for injection should only be given by infusion through a catheter placed in a vein (intravenous infusion) using an infusion pump.
- Your first treatment will be given to you by your healthcare provider or nurse. This is so your healthcare provider can monitor you and find the best dose for you.
- If your healthcare provider decides that you or your caregiver can give infusions of epoprostenol sodium for injection at home, you or your caregiver will receive training on the right way to mix and infuse epoprostenol sodium for injection. Do not try to infuse epoprostenol sodium for injection until you have been shown the right way to infuse epoprostenol sodium for injection by your healthcare provider.
- Treatment will be needed for a long period of time, possibly years. You must be able to accept and care for a catheter and infusion pump in order to be treated with epoprostenol sodium for injection.
- Use epoprostenol sodium for injection exactly as your healthcare provider tells you to.
- Do not change your dose or stop your infusion without talking to your healthcare provider. Stopping epoprostenol sodium for injection suddenly can cause serious side effects.
- You should have a backup infusion pump and extra supplies needed for your infusion of epoprostenol sodium for injection.
- Follow your healthcare provider’s instructions for taking blood thinner medicines, if prescribed for you.
- Before you use epoprostenol sodium for injection, you must mix (reconstitute) epoprostenol sodium for injection powder with a diluent. **STERILE DILUENT for epoprostenol sodium for injection (comes in a glass bottle).**

Do not mix epoprostenol sodium for injection with any other diluent. You must use STERILE DILUENT for epoprostenol sodium for injection.
See “**How should I store and use epoprostenol sodium for injection?**” for more information about how to use and store epoprostenol sodium for injection the right way.

- A mixed solution of epoprostenol sodium for injection is clear and colorless. Do not use epoprostenol sodium for injection if the mixed solution looks discolored or cloudy, or if the solution has flakes or

particles in it.

Using more than the prescribed dose of epoprostenol sodium for injection can lead to death. If you use more than the prescribed dose of epoprostenol sodium for injection, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of epoprostenol sodium for injection?
Epoprostenol sodium for injection can cause serious side effects, including:

- **Fluid in your lungs (pulmonary edema)**. If you develop pulmonary edema after starting epoprostenol sodium for injection, your healthcare provider will stop your treatment and you should not receive epoprostenol sodium for injection again.
- **Worsening symptoms of pulmonary arterial hypertension (PAH) with a sudden decrease in the dose of epoprostenol sodium for injection**. Do not change your dose of epoprostenol sodium for injection or stop your infusion without talking to your healthcare provider. If you suddenly stop or decrease your dose of epoprostenol sodium for injection you may develop worsening symptoms of your PAH, including shortness of breath, dizziness, weakness, or loss of strength.
- **Widening of your blood vessels (vasodilation)**. Vasodilation reactions can happen after you start epoprostenol sodium for injection. These reactions are common and may cause low blood pressure (hypotension), flushing, nausea, vomiting, dizziness, and headache. Your healthcare provider should check your blood pressure regularly during treatment with epoprostenol sodium for injection, especially when you start epoprostenol sodium for injection and after your dose is changed.
- **Increased risk for bleeding**. Epoprostenol sodium for injection affects how well your blood clots, so your risk for bleeding is increased. This is especially true if you have other risk factors for bleeding. Tell your healthcare provider if you develop any unusual bruising or bleeding.

The most common side effects of epoprostenol sodium for injection include:

- dizziness
- jaw pain
- headache
- muscle or bone pain
- nausea or vomiting

These are not all the possible side effects of epoprostenol sodium for injection. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store and use epoprostenol sodium for injection?

- Store epoprostenol sodium for injection powder at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect epoprostenol sodium for injection powder from light. Keep unopened vial of epoprostenol sodium for injection in the carton until you are ready to mix.
- Store the STERILE DILUENT for epoprostenol sodium for injection at room temperature, 68°F to 77°F (20°C to 25°C). Do not freeze.
- **Vial of STERILE DILUENT for epoprostenol sodium for injection is for one-time use only.** Throw away any unused diluent.
- Throw away any vials of epoprostenol sodium for injection powder, STERILE DILUENT for epoprostenol sodium for injection that are out of date or that you no longer need.

How to store mixed solutions of epoprostenol sodium for injection:

- Once epoprostenol sodium for injection and the diluent are mixed together, you may use right away or store in the refrigerator. Refrigerate at 36°F to 46°F (2°C to 8°C).
- Protect the mixed solution of epoprostenol sodium for injection from light until you are ready to use it.
- **Do not freeze mixed solutions. Throw away any mixed solution that has been frozen.**

If you are using STERILE DILUENT for epoprostenol sodium for injection (comes in a glass bottle) for mixing:

- **If the mixed solution will be used at room temperature:**

- Use the mixed solution over a period of **no longer than 8 hours** after mixing **if not stored in the refrigerator**.
- If the mixed solution has been stored in the refrigerator, infuse it over a period of **no longer than 8 hours after removing it from the refrigerator**.
- You may store the mixed solution for up to **40 hours** in the refrigerator.
- **Throw away any mixed solution if it has been refrigerated for more than 40 hours.**

- **If the mixed solution will be used with a cold pouch:**

- You may store the mixed solution in the refrigerator for **up to 24 hours**.
- Take the mixed solution out of the refrigerator and use it with the cold pouch over a period of **no longer than 24 hours. Change the cold pouch every 12 hours.**
  The mixed solution may be kept either in the refrigerator or in the cold pouch, or a combination of the two, for no more than 48 hours. After 48 hours, throw away any mixed solution.

Keep epoprostenol sodium for injection and all medicines out of the reach of children.

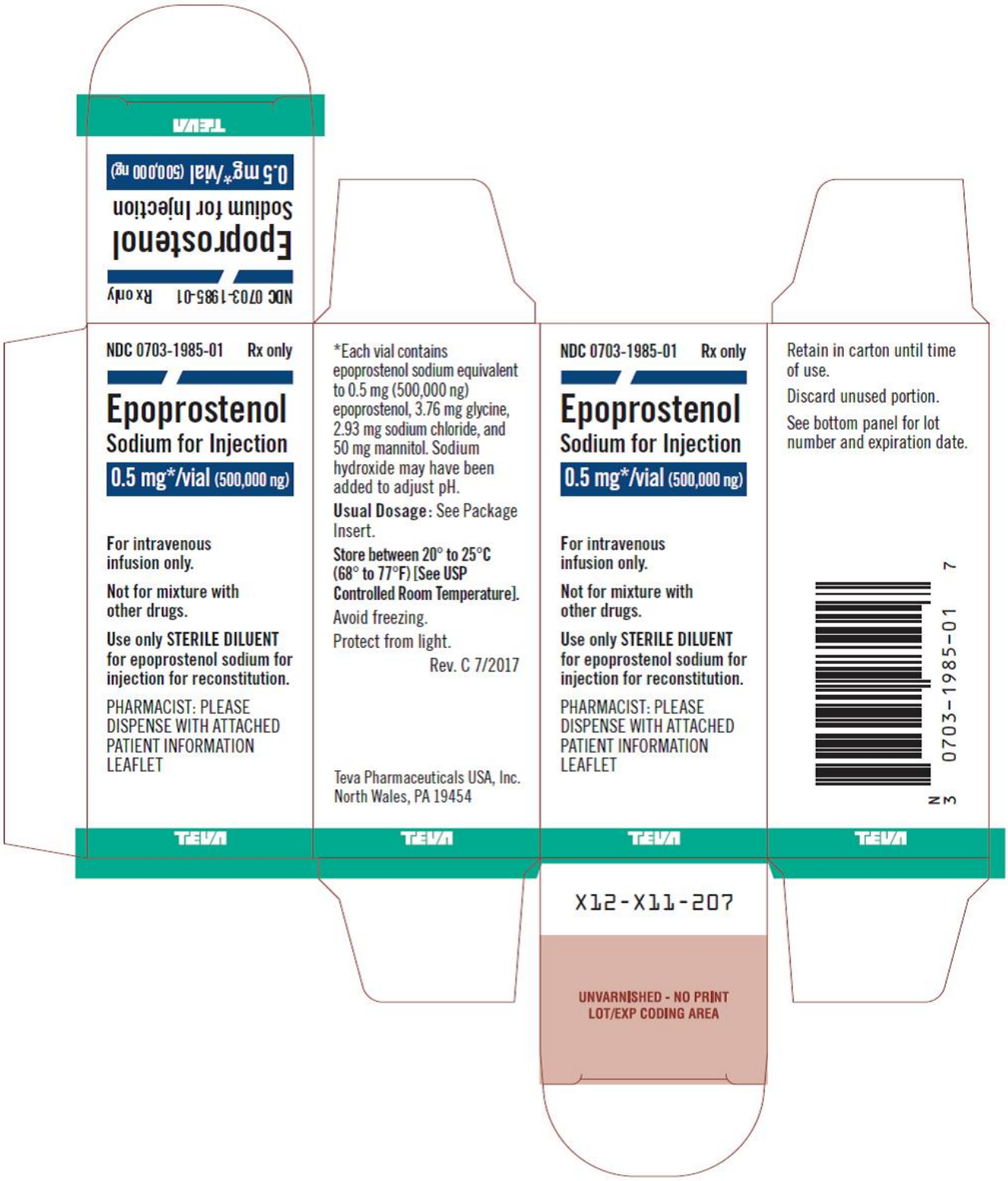
General information about the safe and effective use of epoprostenol sodium for injection
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use epoprostenol sodium for injection for a condition for which it was not prescribed. Do not give epoprostenol sodium for injection to other people, even if they have the same symptoms that you have. It may harm them.
This leaflet summarizes the most important information about epoprostenol sodium for injection. You can ask your healthcare provider or pharmacist for information about epoprostenol sodium for injection that is written for health professionals.
For more information, go to www.tevagenerics.com or call 1-888-838-2872.

What are the ingredients in epoprostenol sodium for injection?
Active ingredient: epoprostenol sodium.
Inactive ingredients: glycine, mannitol, sodium chloride. Sodium hydroxide may have been added.
The STERILE DILUENT for epoprostenol sodium for injection contains: glycine, sodium chloride, sodium hydroxide, and Water for Injection.

Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

This Patient Information has been approved by the U.S. Food and Drug Administration. Rev. B 3/2019

Package/Label Display Panel



Epoprostenol Sodium for Injection 0.5 mg/vial, Carton Text

NDC 0703-1985-01 Rx only

Epoprostenol

Sodium for Injection

0.5 mg*/vial (500,000 ng)

For intravenous

infusion only.

Not for mixture with

other drugs.

Use only STERILE DILUENT

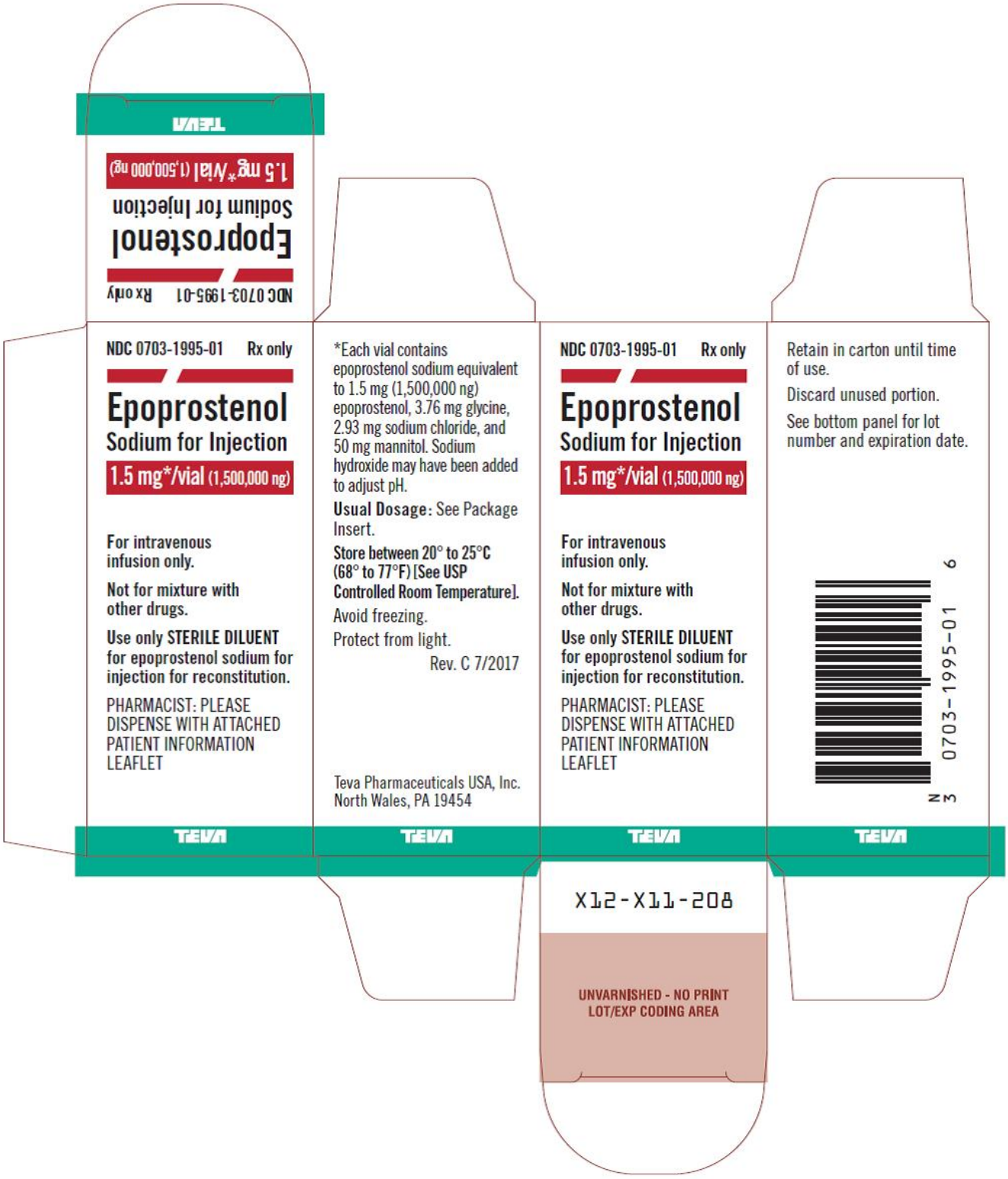
for epoprostenol sodium for injection for reconstitution.

PHARMACIST: PLEASE DISPENSE WITH ATTACHED

PATIENT INFORMATION LEAFLET

TEVA

Package/Label Display Panel



Epoprostenol Sodium for Injection 1.5 mg/vial, Carton Text

NDC 0703-1995-01 Rx only

Epoprostenol

Sodium for Injection

1.5 mg*/vial (1,500,000 ng)

For intravenous

infusion only.

Not for mixture with

other drugs.

Use only STERILE DILUENT

for epoprostenol sodium for injection for reconstitution.

PHARMACIST: PLEASE DISPENSE WITH ATTACHED PATIENT INFORMATION LEAFLET

TEVA

Package/Label Display Panel

Sterile Diluent for Epoprostenol Sodium for Injection 2 x 50 mL Vial Tray Label Text

NDC 0703-9258-09 Rx only

Sterile Diluent

for Epoprostenol Sodium for Injection

50 mL

For reconstitution information see package insert for Epoprostenol Sodium for Injection.

Contains drug diluent for use only with Epoprostenol Sodium for Injection.

PHARMACIST: PLEASE DISPENSE WITH ATTCHED APTIENT INFORMATION LEAFLET

2 Vials

TEVA

EPOPROSTENOL SODIUM

epoprostenol sodium injection, powder, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0703-1985
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
EPOPROSTENOL SODIUM (UNII: 4K04IQ1OF4) (EPOPROSTENOL - UNII:DCR9Z582X0)	EPOPROSTENOL	0.5 mg

Inactive Ingredients	
Ingredient Name	Strength
GLYCINE (UNII: TE7660XO1C)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0703-1985-01	1 in 1 CARTON	04/23/2008	
1		1 in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078396	04/23/2008	

EPOPROSTENOL SODIUM

epoprostenol sodium injection, powder, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0703-1995
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
EPOPROSTENOL SODIUM (UNII: 4K04IQ1OF4) (EPOPROSTENOL - UNII:DCR9Z582X0)	EPOPROSTENOL	1.5 mg

Inactive Ingredients	
Ingredient Name	Strength
GLYCINE (UNII: TE7660XO1C)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:0703-1995-01	1 in 1 CARTON	04/23/2008	
1		1 in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078396	04/23/2008	

STERILE DILUENT

sterile diluent injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0703-9258
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
WATER (UNII: 059QF0KO0R) (WATER - UNII:059QF0KO0R)	WATER	1 mL in 1 mL

Inactive Ingredients

Ingredient Name	Strength
GLYCINE (UNII: TE7660XO1C)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0703-9258-09	2 in 1 TRAY	04/23/2008	
1	NDC:0703-9258-01	50 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078396	04/23/2008	

Labeler - Teva Parenteral Medicines, Inc. (794362533)

Revised: 3/2019 Teva Parenteral Medicines, Inc.