PRODUCT MONOGRAPH

INCLUDING CONSUMER INFORMATION

PrTREPROSTINIL INJECTION

Sterile Solution for Intravenous or Subcutaneous infusion

1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL of treprostinil

(as treprostinil sodium)

Vasodilator

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PrTREPROSTINIL INJECTION

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Subcutaneous or Intravenous	Injection; 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL of treprostinil	metacresol, sodium chloride, sodium citrate dihydrate, sodium hydroxide and water for injection. Hydrochloric acid and sodium hydroxide may have been added to adjust pH

INDICATIONS AND CLINICAL USE

Treprostinil Injection (treprostinil) is indicated for the long-term, subcutaneous or intravenous treatment of pulmonary arterial hypertension (PAH) in NYHA Class III and IV patients who did not respond adequately to conventional therapy.

Treprostinil Injection should be used only by clinicians experienced in the diagnosis and treatment of PAH. Treprostinil Injection is a potent pulmonary and systemic vasodilator. Initiation of Treprostinil Injection must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Treprostinil Injection is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter. Therapy with Treprostinil Injection may be used for prolonged periods, and the patient's ability to administer Treprostinil Injection and care for an infusion system should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Treprostinil Injection.

Geriatrics (> 65 years of age):
Safety and effectiveness in geriatric patients have not been established. (See WARNINGS and PRECAUTIONS, Special Populations, Geriatrics)

Pediatrics (< 16 years of age):
Safety and effectiveness in pediatric patients have not been established. (See WARNINGS and PRECAUTIONS, Special Populations, Pediatrics)

CONTRAINDICATIONS

Treprostinil Injection is contraindicated in patients with known hypersensitivity to the drug, any of its excipients, or to structurally related compounds. For a complete listing of Treprostinil Injection excipients, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General Conditions of Use

Treprostinil Injection is a potent pulmonary and systemic vasodilator. Treprostinil Injection is indicated for subcutaneous or intravenous use only.

Treprostinil Injection should be used only by clinicians experienced in the diagnosis and treatment of PAH.
Dosage adjustments in clinical trials were based on the patient's signs and symptoms of PAH and side effects of Treprostinil Injection. Dosage of Treprostinil Injection should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PAH or the occurrence of intolerable adverse events associated with Treprostinil Injection. (See DOSAGE and ADMINISTRATION.)

The decision to initiate therapy with Treprostinil Injection should be based on the understanding that there is a high likelihood that subcutaneous or intravenous therapy with Treprostinil Injection will be needed for prolonged periods, possibly years, and the patient's ability to administer Treprostinil Injection and care for an infusion system should be carefully considered.

As with any potent vasodilator, abrupt withdrawal or sudden large reductions in dosage of Treprostinil Injection may result in worsening of PAH symptoms. Avoid abrupt withdrawal of Treprostinil Injection if at all possible. Although in clinical trials, no patient death from discontinuation of treprostinil was judged directly attributable to the interruption of the drug, 2 of 11 patients who abruptly discontinued subcutaneous treprostinil therapy died within 24 hours. Although their death may have been related to their deteriorating clinical condition, it seems most appropriate to wean patients from treprostinil. Only 3 of 55 (5%) patients with abrupt disruption of treprostinil developed increased symptoms of PAH, and no patients developed hemodynamic instability. In addition, among patients who discontinued treprostinil abruptly, no relationship has been established between abrupt discontinuation and rebound pulmonary hypertension.

Risk of Catheter-Related Blood Stream Infections

Chronic intravenous infusions of Treprostinil Injection are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. Therefore, continuous subcutaneous infusion (undiluted) is the preferred mode of administration.

Carcinogenesis and Mutagenesis

Long-term studies in humans have not been performed to evaluate the carcinogenic potential of treprostinil. (See TOXICOLOGY for results from animal studies)

Endocrine and Metabolism

Obese subjects (BMI >30.0 kg/m^2) clear treprostinil at a slower rate. Since doses of Treprostinil Injection are increased from very low initial doses to doses that improve disease symptoms while minimizing adverse effects, dosing to ideal body weight in obese patients should not be necessary.

Hepatic/Biliary/Pancreatic

An acute study of treprostinil administered subcutaneously at a dose of 10 ng/kg/min for 150 minutes was conducted in nine patients with portopulmonary hypertension and stable, mild or moderate hepatic dysfunction. Treprostinil was well tolerated and improved cardiopulmonary hemodynamics. Hepatic dysfunction reduced plasma clearance of treprostinil by up to 80% compared to healthy adult volunteers primarily by lowering the volume of distribution without affecting plasma half-life.

Treprostinil Injection should be increased more conservatively in patients with hepatic dysfunction, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic function. These patients should be closely monitored for signs and symptoms or emergence of adverse reactions due to excess Treprostinil Injection. Treprostinil has not been studied in patients with severe hepatic dysfunction.

Renal
No studies have been performed in patients with renal impairment. Treprostinil is not excreted to any significant degree by the kidney, however, its metabolites are excreted mainly by the kidney. Based on the individual patient dose titration recommended for Treprostinil Injection, doses of Treprostinil Injection should be increased more conservatively in patients with renal insufficiency.

Special Populations

Pregnant Women: The extent of exposure in pregnancy during clinical trials is very limited. There are no adequate and well controlled studies in pregnant women. No developmental toxicity was seen in rats at any dose of treprostinil up to 900 ng/kg/min and in rabbits at 50 ng/kg/min. In pregnant rabbits, developmental toxicity characterized by minimal increases in fetal skeletal variations per litter was observed at doses of 150 and 300 ng/kg/min and was associated with maternal toxicity.

Nursing Women: It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (<16 years of age): Safety and effectiveness in pediatric patients have not been established. Clinical studies of treprostinil did not include sufficient numbers of patients aged <16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

Geriatrics (> 65 years of age): Clinical studies of treprostinil did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Overview

Interpretation of adverse events (AEs) reported during clinical trials should be undertaken with an awareness of expected events attributable to the progression of the underlying disease, to Treprostinil Injection, and/or to the drug delivery system.

Interpretation of adverse events is complicated by the clinical features of PAH, which are similar to some of the pharmacological effects of treprostinil (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, right ventricular heart failure and pallor. During clinical trials with subcutaneous infusion of treprostinil, infusion site pain and reaction were the most common adverse events among those treated with treprostinil. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash.

Adverse reactions included headache, diarrhea, vomiting, jaw pain, swelling/edema, flushing/ vasodilatation, muscle or joint pain, low systemic blood pressure, pain in extremities and nausea, and these are generally considered to be related to the pharmacologic effects of treprostinil, whether administered subcutaneously or intravenously.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions During Chronic Treatment: In an effort to separate the adverse reactions on treprostinil from those of the underlying disease, Table 1 lists adverse events that occurred at a rate greater than 1% in PAH patients participating in placebo-controlled trials of subcutaneous treprostinil.

Table 1: Frequency of Adverse Events Regardless of Attribution Occurring in >1% of Patients with PAH in Placebo-Controlled Studies of Subcutaneous Treprostinil

	Treprostinil (N=236) N (%)	**Placebo (N=233) N (%)**
OCCURRENCE MORE COMMON WITH TREPROSTINIL		
Skin and Appendages		
Infusion site pain	200 (84.7)	62 (26.6)
Infusion site reaction	196 (83.1)	62 (26.6)
Rash	32 (13.6)	26 (11.2)
Pruritus	19 (8.1)	15 (6.4)
Contact Dermatitis	3 (1.3)	1 (0.4)
Sweating	3 (1.3)	1 (0.4)
General (Body as Whole)		
Headache	64 (27.1)	54 (23.2)
Jaw pain	31 (13.1)	11 (4.7)

Pain	28 (11.9)	25 (10.7)
Infection	21 (8.9)	20 (8.6)
Asthenia	11 (4.7)	7 (3.0)
Flu Syndrome	11 (4.7)	9 (3.9)
Overdose	3 (1.3)	0 (0.0)
Injection Site Reaction	3 (1.3)	0 (0.0)
Gastrointestinal (Digestive)		
Diarrhea	58 (24.6)	36 (15.5)
Nausea	52 (22.0)	41 (17.6)
Anorexia	11 (4.7)	4 (1.7)
Nausea and vomiting	7 (3.0)	2 (0.9)
Melena	5 (2.1)	0 (0.0)
Rectal Hemorrhage	3 (1.3)	0 (0.0)
Cardiovascular		
Hypotension	9 (3.8)	6 (2.6)
Tachycardia	4 (1.7)	3 (1.3)
Palpitation	3 (1.3)	2 (0.9)
Hematologic and Lymphatic		
Anemia	3 (1.3)	3 (1.3)
Metabolic and Nutritional		
Edema	21 (8.9)	6 (2.6)
Hypokalemia	5 (2.1)	0 (0.0)
Gout	3 (1.3)	1 (0.4)
Dehydration	3 (1.3)	0 (0.0)
Muscoskeletal		
Myalgia	3 (1.3)	1 (0.4)
Neurological/Nervous		
Vasodilatation	25 (10.6)	11 (4.7)
Dizziness	21 (8.9)	19 (8.2)
Insomnia	14 (5.9)	8 (3.4)
Anxiety	7 (3.0)	6 (2.6)
Paresthesia	3 (1.3)	2 (0.9)
Respiratory		
Epistaxis	10 (4.2)	4 (1.7)
Rhinitis	5 (2.1	5 (2.1)
Hypoxia	4 (1.7)	1 (0.4)
Urogenital		
Urinary Tract Infection	4 (1.7)	3 (1.3)
OCCURRENCE MORE COMMON WITH PLACEBO		
Skin and Appendages		
Infusion site bleed/bruise	79 (33.5)	102 (43.8)

Hematologic and Lymphatic		
Ecchymosis	9 (3.8)	27 (11.6)
Body		
Chest Pain	10 (4.2)	20 (8.6)
Abdominal Pain	8 (3.4)	10 (4.3)
Back Pain	6 (2.5)	11 (4.7)
Fever	6 (2.5)	10 (4.3)
Cellulitus	3 (1.3)	3 (1.3)
Malaise	2 (0.8)	3 (1.3)
Viral Infection	1 (0.4)	3 (1.3)
Neck Pain	2 (0.8)	5 (2.1)
Cardiovascular		
Heart Failure	7 (3.0)	17 (7.3)
Hemorrhage	7 (3.0)	13 (5.6)
Syncope	7 (3.0)	12 (5.2)
Bradycardia	3 (1.3)	3 (1.3)
Gastrointestinal (Digestive)		
Vomiting	12 (5.1)	14 (6.0)
Dyspepsia	3 (1.3)	6 (2.6)
Metabolic and Nutritional		
Peripheral Edema	11 (4.7)	16 (6.9)
Neurological/Nervous		
Depression	3 (1.3)	6 (2.6)
Nervousness	1 (0.4)	3 (1.3)
Respiratory		
Pharyngitis	13 (5.5)	21 (9.0)
Cough	7 (3.0)	19 (8.2)
Dyspnea	8 (3.4)	19 (8.2)
Sinusitis	4 (1.7)	9 (3.9)
Pulmonary Hypertension	4 (1.7)	6 (2.6)
Hemoptysis	4 (1.7)	5 (2.1)
Bronchitis	2 (0.8)	6 (2.6)
Urogenital		
Hematuria	2 (0.8)	3 (1.3)
Muscoskeletal		
Leg Cramps	2 (0.8)	5 (2.1)
Arthralgia	2 (0.8)	3 (1.3)

Adverse Event Description as COSTART Preferred Term

Table 2 lists all adverse reactions reported in controlled clinical trials of patients with PAH, that were significantly more frequently encountered in the subcutaneous treprostinil group than in the placebo group, regardless of attribution.

Table 2: Adverse Reactions Occurring Significantly (p<0.1) More Frequently in the Subcutaneous Treprostinil Group than in the Placebo Group, Regardless of Attributability

Adverse Reaction Description, as COSTART Preferred Term	Number of Events Treprostinil Group / Placebo Group	p-value
Any adverse reaction	231 / 218	0.0173
Infusion site pain	200 / 62	<0.0001
Infusion site reaction	196 / 62	<0.0001
Diarrhea	58 / 36	0.0091
Jaw pain	31 / 11	0.0010
Vasodilatation	25 / 11	0.0127
Edema	21 / 6	0.0026
Anorexia	11 / 4	0.0592
Epistaxis	10 / 4	0.0904
Nausea and vomiting	7 / 2	0.0909
Hypokalemia	5 / 0	0.0316
Melena	5 / 0	0.0316

Adverse Events Attributable to the Drug Delivery System: In controlled studies of treprostinil administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% treprostinil, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 treprostinil, 4 placebo) reported non-serious adverse events resulting in infusion system complications. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration, although in some cases PAH symptoms reappeared. These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, or straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration. In addition to these adverse events due to the drug delivery system during subcutaneous administration, the following adverse events may be attributable to the IV mode of infusion including arm swelling, paresthesias, hematoma and pain.

There are a limited number of clinical studies with treprostinil administered via central venous infusion. The overall adverse event profile in these intravenous studies is similar to that of treprostinil administered subcutaneously, as would be expected based on the established bioequivalence of subcutaneous and intravenous routes of administration. However, as with any chronic indwelling central venous catheter, there are risks associated with delivery of therapy by this route. These risks include pain at the catheter insertion site, local infection, sepsis, thrombus formation and subsequent line occlusion, and malfunctions in the delivery system resulting in an inadvertent bolus of or a reduction in treprostinil which could produce symptoms related to excess or insufficient treprostinil, respectively.

In an open-label study of intravenous treprostinil (n=47) there were seven catheter-related line infections during approximately 35 patient years, or about 1 blood stream infection (BSI) event

per 5 years of use. A Centers for Disease Control survey of seven sites that used intravenous treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use.

Among patients randomized in a 12-week placebo-controlled study in India to either intravenous treprostinil (n=30) or placebo (n=15), vomiting, headache, diarrhea, jaw pain and extremity pain were more common in patients treated with treprostinil than placebo. Serious AEs were no more common in the treprostinil group than the placebo group, and included sepsis, congestive heart failure, pulmonary embolism, thrombophlebitis, catheter related complications, pseudomonal sepsis and pseudomonas infection.

Post-Market Adverse Drug Reactions
In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of treprostinil. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting, and potential connection to treprostinil. These events are thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia, bone pain, pruritus, dizziness, arthralgia, myalgia, and muscle spasm. Treprostinil inhibits platelet aggregation and increases the risk of bleeding. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

DRUG INTERACTIONS

Overview
In clinical studies, no untoward clinical manifestations have been observed in patients in whom treprostinil was used concurrently with the following classes of drugs: Anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, opioids and corticosteroids.

Antihypertensive Agents or other Vasodilators
Additional reductions in blood pressure may occur when Treprostinil Injection is administered with diuretics, antihypertensive agents, or other vasodilators.

Anticoagulants and Antiplatelet Agents
When antiplatelet agents or anticoagulants are used concomitantly with Treprostinil Injection there is the potential for increased risk of bleeding due to the antiplatelet effect of treprostinil. However, patients receiving treprostinil in clinical trials were maintained on anticoagulants without evidence of increased bleeding. Treprostinil investigated in healthy volunteers had no effect in vivo on warfarin pharmacodynamics as measured by the effect on INR. Treprostinil also had no effect on pharmacokinetics of either the R- or S-enantiomer of warfarin.

Pharmacokinetics

Effect of Cytochrome P450 Inhibitors and Inducers on Treprostinil
Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme

inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It has not been determined if the safety and efficacy of treprostinil by the parenteral (subcutaneously or intravenously) route are altered by inhibitors or inducers of CYP2C8.

Interaction potential with alcohol has not been established.

Modest interaction was observed between treprostinil and furosemide. Treprostinil Injection dose reduction in patients receiving furosemide is not recommended, although patients should be monitored for excess adverse effects of Treprostinil Injection.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Patients with hepatic impairment (See Dosage in Patients with Hepatic Impairment).

Recommended Dose and Dosage Adjustment
Treprostinil Injection can be administered without further dilution for subcutaneous administration, or diluted for intravenous infusion with 0.9% Sodium Chloride Injection or Sterile Water for Injection at concentrations as low as 0.004 mg/mL prior to administration.

Initial Dose: Treprostinil Injection is administered by continuous subcutaneous or continuous intravenous infusion. Treprostinil Injection is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, because of systemic effects, reduce the infusion rate to 0.625 ng/kg/min.

Dosage Adjustments: The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Treprostinil Injection (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of 1.25 ng/kg/min per week for the first four weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion depending on clinical response. Dosage adjustment may be undertaken more often if tolerated and adjusted based on PAH signs and symptoms and Treprostinil Injection side effects. Dose-related symptoms may necessitate a decrease in infusion rate; however, the event may resolve without dosage adjustment. Should an adverse event worsen and/or become intolerable, the infusion rate should be reduced, or infusion should be discontinued. Abrupt cessation of infusion should be avoided (See WARNINGS AND PRECAUTIONS). Restarting a Treprostinil Injection infusion within a few hours after interruption can be done using the same dose rate. Interruptions for longer periods may require the dose of Treprostinil Injection to be re-titrated.

Effects of Other Drugs on Treprostinil: Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) increases exposure (both Cmax and AUC) to treprostinil. Treprostinil Injection dose reduction should be considered. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) decreases exposure to treprostinil. Treprostinil Injection dose increases should be considered.

Dosage in Patients with Hepatic Impairment: In patients with mild to moderate hepatic insufficiency, decrease the initial dose of Treprostinil Injection to 0.625 ng/kg/min ideal body weight. The dose should be increased more conservatively in patients with hepatic dysfunction, and these patients should be closely monitored for signs and symptoms or emergence of adverse events due to excess Treprostinil Injection. Treprostinil has not been studied in patients with severe hepatic insufficiency.

Missed Dose

As with any potent vasodilator, abrupt withdrawal or sudden large reductions in dosage of Treprostinil Injection may result in worsening of PAH symptoms. Abrupt withdrawal of Treprostinil Injection should be avoided if at all possible. Although in clinical trials, no patient death from discontinuation of treprostinil was judged directly attributable to the interruption of the drug, 2 of 11 patients who abruptly discontinued treprostinil therapy died within 24 hours. Although their death may have been related to their deteriorating clinical condition, it seems most appropriate to wean patients from treprostinil. Only 3 of 55 (5%) patients with abrupt disruption of treprostinil developed increased symptoms of PAH, and no patients developed hemodynamic instability. In addition, among patients who discontinued treprostinil abruptly, no relationship has been established between abrupt discontinuation and rebound pulmonary hypertension.

Restarting a treprostinil infusion within a few hours after an interruption can be done using the same dose rate. Interruptions for longer periods may require the dose of treprostinil to be re-titrated.

Administration

Treprostinil Injection should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, discoloration, or leakage should not be used. Discard unused portion.

Treprostinil Injection is administered using a suitable ambulatory infusion pump that should:
(1) be small and lightweight,
(2) be able to adjust infusion rates in approximately 0.002 mL/hr,
(3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms,
(4) have delivery accuracy of ±6% or better, and
(5) be positive pressure driven.
The reservoir should be made of polyvinyl chloride, polypropylene, or glass.

Subcutaneous Infusion: Treprostinil Injection is administered subcutaneously by continuous infusion without further dilution, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets.

For subcutaneous infusion, Treprostinil Injection is delivered without further dilution at a calculated Subcutaneous Infusion Rate (mL/hr) based on a patients Dose (ng/kg/min), Weight (kg), and the Vial Strength (mg/mL) of Treprostinil Injection being used. During use, a single reservoir (syringe) of undiluted Treprostinil Injection can be administered up to 72 hours at 37°C.

The Subcutaneous Infusion rate is calculated using the following formula:

$$\textbf{Subcutaneous Infusion Rate (mL/hr)} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006*}}{\textbf{Treprostinil Injection Vial Strength} \text{ (mg/mL)}}$$

*Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng

Example calculations for Subcutaneous Infusion are as follows:

Example 1:
For a 60 kg person at the recommended initial dose of 1.25 ng/kg/min using the 1 mg/mL Treprostinil Injection Vial Strength, the infusion rate would be calculated as follows:

$$\textbf{Subcutaneous Infusion Rate (mL/hr)} = \frac{\textbf{1.25} \text{ ng/kg/min} \times \textbf{60} \text{ kg} \times \textbf{0.00006}}{\textbf{1} \text{ mg/mL}} = \textbf{0.005} \text{ mL/hr}$$

Example 2:
For a 65 kg person at a dose of 40 ng/kg/min using the 5 mg/mL Treprostinil Injection Vial Strength, the infusion rate would be calculated as follows:

$$\textbf{Subcutaneous Infusion Rate (mL/hr)} = \frac{\textbf{40} \text{ ng/kg/min} \times \textbf{65} \text{ kg} \times \textbf{0.00006}}{\textbf{5} \text{ mg/mL}} = \textbf{0.031} \text{ mL/hr}$$

Intravenous Infusion: Treprostinil Injection must be diluted with Sterile Water for Injection, or 0.9% Sodium Chloride Injection prior to administration. Diluted Treprostinil Injection is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. If clinically necessary, a temporary peripheral intravenous cannula, preferably placed in a large vein, may be used for short term administration of Treprostinil Injection. Use of a peripheral intravenous infusion for more than a few hours may be associated with an increased risk of thrombophlebitis. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The infusion set should also contain 0.22 or 0.2 micrometer pore size in-line filter and an anti-siphon valve.

Diluted Treprostinil Injection has been shown to be stable at ambient temperature for up to 48 hours using 0.9% Sodium Chloride Injection or Sterile Water for Injection as the diluent at concentrations as low as 0.004 mg/mL.

When using an appropriate infusion pump and reservoir, a predetermined intravenous infusion rate should first be selected to allow for a desired infusion period length of up to 48 hours between system changes. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL. With this selected Intravenous Infusion Rate (mL/hr) and the patient's Dose

(ng/kg/min) and Weight (kg), the Diluted Intravenous Treprostinil Injection Concentration (mg/mL) can be calculated using the following formula:

Step 1

$$\textbf{Diluted Intravenous Treprostinil Injection Concentration} \text{ (mg/mL)} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006}}{\textbf{Intravenous Infusion Rate} \text{ (mL/hr)}}$$

The volume of Treprostinil Injection needed to make the required Diluted Intravenous Treprostinil Injection Concentration for the given reservoir size can then be calculated using the following formula:

Step 2

$$\textbf{Volume of Treprostinil Injection} \text{ (mL)} = \frac{\textbf{Diluted Intravenous Treprostinil Injection Concentration} \text{ (mg/mL)}}{\textbf{Treprostinil Injection Vial Strength} \text{ (mg/mL)}} \times \textbf{Total Volume of Diluted Treprostinil Injection Solution in Reservoir} \text{ (mL)}$$

The calculated volume of Treprostinil Injection is then added to the reservoir along with the sufficient volume of diluent to achieve the desired total volume in the reservoir.

Example calculations for Intravenous Infusion are as follows:

Example 3:
For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 mL/hr and a reservoir of 50 mL, the Diluted Intravenous Treprostinil Injection Solution Concentration would be calculated as follows:

Step1

$$\textbf{Diluted Intravenous Treprostinil Injection Concentration} \text{ (mg/mL)} = \frac{\textbf{5 ng/kg/min X 60 kg X 0.00006}}{\textbf{1 mL/hr}} = \textbf{0.018 mg/mL (18,000 ng/mL)}$$

The volume of Treprostinil Injection (using 1 mg/mL Vial Strength) needed for a total Diluted Treprostinil Injection Concentration of 0.018 mg/mL and a total volume of 50 mL would be calculated as follows:

Step 2

$$\textbf{Volume of Treprostinil Injection (mL)} = \frac{\textbf{0.018 mg/mL}}{\textbf{1 mg/mL}} \textbf{ X 50 mL} = \textbf{0.9 mL}$$

The diluted intravenous Treprostinil Injection concentration for the person in Example 3 would thus be prepared by adding 0.9 mL of 1 mg/mL Treprostinil Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 mL in the reservoir. The pump flow rate for this example would be set at 1 mL/hr.

Example 4:

For a 75 kg person at a dose of 30 ng/kg/min, with a predetermined intravenous infusion rate of 2 mL/hr, and a reservoir of 100 mL, the diluted intravenous Treprostinil Injection solution concentration would be calculated as follows:

Step 1

$$\textbf{Diluted Intravenous Treprotinil Injection Concentration (mg/mL)} = \frac{\textbf{30 ng/kg/min X 75 kg X 0.00006}}{\textbf{2 mL/hr}} = \textbf{0.0675 mg/mL (67,500 ng/mL)}$$

The volume of Treprostinil Injection (using 2.5 mg/mL Vial Strength) needed for a total diluted Treprostinil Injection concentration of 0.0675 mg/mL and a total volume of 100 mL would be calculated as follows:

Step 2

$$\textbf{Volume of Treprostinil Injection (mL)} = \frac{\textbf{0.0675 mg/mL}}{\textbf{2.5 mg/mL}} \textbf{ X 100 mL} = \textbf{2.7 mL}$$

The diluted intravenous Treprostinil Injection concentration for the person in Example 4 would thus be prepared by adding 2.7 mL of 2.5 mg/mL Treprostinil Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 100 mL in the reservoir. The pump flow rate for this example would be set at 2 mL/hr.

OVERDOSAGE

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

Signs and symptoms of overdose with treprostinil during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of treprostinil

In controlled clinical trials, seven patients received some level of overdose and in chronic, open-label follow-on treatment, seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of treprostinil, errors in pump programmed rate of administration, and prescription of incorrect dose. The amount of excess treprostinil actually administered varied in each patient. Three placebo patients in controlled clinical trials were inadvertently administered treprostinil with doses initiated at 8.5, 10 and 15 ng/kg/min, respectively. Six patients received excess treprostinil due to incorrect pump settings (excess doses ranged from two to forty-six times their prescribed dose). The remaining five patients received excess treprostinil as a result of accidental bolus administration while in the process of changing syringes or tubing. Typical symptoms elicited were expected pharmacologic effects and included flushing, headache, hypotension, nausea, vomiting and diarrhea. The symptoms resolved with reduction of treprostinil dose or withholding treprostinil for a short time. In only two cases did excess delivery of treprostinil produce an event of substantial hemodynamic concern (hypotension, near-syncope). No deaths occurred as a result of overdose.

One pediatric patient was accidentally administered 7.5 mg of treprostinil via a central venous catheter. Symptoms included flushing, headache, nausea, vomiting, hypotension and seizure-like activity with loss of consciousness lasting several minutes. The patient subsequently recovered.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Treprostinil is a tricyclic benzindene analogue of prostacyclin (PGI2). The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. The effect of treprostinil on heart rate in animals varies with dose. No major effects on cardiac conduction have been observed.

Pharmacodynamics

Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Hemodynamic Effects: Acute infusion of treprostinil at 10 ng/kg/min intravenously for 75 minutes followed by a 10 ng/kg/min infusion subcutaneously for 150 minutes, in patients with primary pulmonary hypertension produced increases in cardiac index (CI) and mixed venous oxygen saturation (SvO_2), and decreases in mean pulmonary arterial pressure (PAPm), mean

right atrial pressure (RAPm) and pulmonary vascular resistance indexed (PVRI), with little effect on mean systemic arterial pressure (SAPm), or heart rate (HR).
Chronic continuous, subcutaneous infusion of treprostinil in NYHA Class II, III, or IV patients with PAH was studied in two identical, 12-week, double-blind, placebo-controlled, multicenter, parallel-group, randomized trials comparing treprostinil plus conventional therapy to conventional therapy alone. Dosage of treprostinil averaged 9.3 ng/kg/min at Week 12.

The hemodynamic effects from the two placebo-controlled studies are shown in Table 3. The hemodynamic effects after chronic therapy with treprostinil were generally consistent with the pharmacological effects seen acutely. There were statistically significant increases in CI and SvO_2, and statistically significant decreases in PAPm, RAPm, PVRI, and SVRI in patients treated with treprostinil for 12 weeks compared to patients treated with placebo. Heart rate and SAPm were unchanged. In patients with pulmonary hypertension, elevated RAPm and PAPm, and reduced CO and SvO2 are predictive of mortality.

Table 3: Hemodynamics During Chronic Subcutaneous Administration of Subcutaneous Treprostinil in Patients with PAH

	Baseline		**Mean Change from Baseline at Week 12**	
Hemodynamic Parameter	**Treprostinil (N=204-231)**	**Placebo (N=215-235)**	**Treprostinil (N=163-199)**	**Placebo (N=182-215)**
CI (L/min/m^2)	2.37 ± 0.06	2.24 ± 0.05	+0.12 ± 0.04*	-0.06 ± 0.04
PAPm (mmHg)	61.8 ± 1.16	59.9 ± 0.96	-2.3 ± 0.51*	+0.7 ± 0.58
RAP (mmHg)	10.3 ± 0.38	10.0 ± 0.39	-0.5 ± 0.36*	+1.4 ± 0.33
PVRI (mmHg/L/min/m^2)	26.51 ± 0.97	25.11 ± 0.87	-3.54 ± 0.64*	+1.20 ± 0.57
SVRI (mmHg/L/min/m^2)	37.87 ± 1.05	39.23 ± 1.02	-3.54 ± 0.96*	-0.80 ± 0.85
SvO_2 (%)	61.5 ± 0.70	60.2 ± 0.77	+2.0 ± 0.76*	-1.4 ± 0.65
SAPm (mmHg)	89.6 ± 0.92	90.7 ± 0.89	-1.7 ± 0.86	-1.0 ± 0.91
HR (bpm)	82.4 ± 0.83	82.1 ± 0.97	-0.5 ± 0.80	-0.8 ± 0.74

*Denotes statistically significant difference between treprostinil and placebo, $p \leq 0.0005$.
CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular pressure indexed; RAPm = mean right atrial pressure, SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO2 = mixed venous oxygen saturation, HR = heart rate.

Pharmacokinetics

Table 4 provides data from a randomized, two-period, cross-over study of treprostinil in normal volunteers. In this study, subcutaneous and intravenous administration of treprostinil (10 ng/kg/min) for 72 hours demonstrated bioequivalence at steady-state, between 48 and 72 hours.

Table 4: Summary of Pharmacokinetic Parameters of Treprostinil

Route of Treprostinil Administration (10ng/kg/min)	$C_{max\ ss}$ (ng/mL)	$t_{½}$ (h) Geom. Mean	$t_{½}$ (h) Mean	AUC_{ss} (hr*ng/mL)	Clearance mL/kg/h	Volume of distribution (L/kg)
Subcutaneous	1.39	4.13	4.61	27.63	550.8	3.28
Intravenous	1.47	3.45	4.41	25.69	565.8	2.82

Steady-state (ss) comparisons were made based on extensive plasma sampling between 48 and 72 hours.

In a [^{14}C] treprostinil mass balance and metabolic fate study in healthy volunteers, 78.6% and 13.4% of the subcutaneous radioactive dose were recovered in the urine and feces, respectively, over a period of 224 hours. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% of the dose administered. These five metabolites accounted for a combined total of 64.4%. Three metabolites are products of oxidation of the 3-hydroxyloctyl side chain, one is glucuronide conjugate (treprostinil glucuronide) and one is unidentified. Only 3.7% of the dose was recovered in the urine as unchanged parent drug.
In a chronic pharmacokinetic study in normal volunteers with chronic subcutaneous treprostinil doses ranging from 2.5 to 15 ng/kg/min, steady-state plasma treprostinil concentrations achieved peak levels twice (at 1 a.m. and 10 a.m., respectively) and achieved through levels twice (at 7 a.m. and 4 p.m., respectively). The peak concentrations were ~20% to 30% higher than trough concentrations. Dose adjustments are not deemed to be necessary due to diurnal variation.

Absorption: Treprostinil is rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2 mcg/L.

Distribution: The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Treprostinil at in vitro concentrations ranging from 330-10,000 mcg/L was 91% bound to human plasma protein.

Metabolism: Treprostinil is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of in vitro human hepatic cytochrome P450 studies, treprostinil does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether treprostinil induces these enzymes has not been studied.

Excretion: The elimination of treprostinil is biphasic, with a terminal half-life of approximately 4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 L/h for a 70 kg ideal body weight person.

Special Populations and Conditions

Hepatic Insufficiency: (See WARNINGS and PRECAUTIONS, Hepatic/Biliary/Pancreatic)

Renal Insufficiency: (See WARNINGS and PRECAUTIONS, Renal)

STORAGE AND STABILITY

Treprostinil Injection should be stored at room temperature at 15°C to 30°C. The products are to be stored in the original carton packaging and protected from light. A single vial of Treprostinil Injection should be used for no more than 30 days after the initial puncture of the rubber stopper.

Treprostinil Injection can be administered without further dilution for subcutaneous administration, or diluted for intravenous infusion with Sterile Water for Injection, or 0.9% Sodium Chloride Injection prior to administration to concentrations as low as 0.004 mg/mL. See Table 5 for storage and administration time limits.

Table 5: Storage

Route	Diluent	Storage limits	Administration limits
SC	None	Per vial label	72 hours at 37°C
IV	Sterile water for injection 0.9% Sodium Chloride for injection	4 hours at room temperature or 24 hours refrigerated	48 hours at 40°C

SPECIAL HANDLING INSTRUCTIONS

Avoid contact with skin or eyes. For skin contact, wash affected area immediately with soap and water and contact physician. For eye contact, flush eyes immediately with large amounts of water and contact physician.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Treprostinil Injection (treprostinil) for subcutaneous or intravenous use is supplied in:
20 mg/ 20 mL (1 mg/mL) Multidose vial: 20 mL clear glass vial with 20 mm dark grey rubber stopper and 20 mm yellow MT flip-off seal. Each carton contains one 20 mL vial.

50 mg/ 20 mL (2.5 mg/mL) Multidose vial: 20 mL clear glass vial with 20 mm dark grey rubber stopper and 20 mm blue MT flip-off seal. Each carton contains one 20 mL vial.

100 mg/ 20 mL (5 mg/mL) Multidose vial: 20 mL clear glass vial with 20 mm dark grey rubber stopper and 20 mm green MT flip-off seal. Each carton contains one 20 mL vial.

200 mg/ 20 mL (10 mg/mL) Multidose vial: 20 mL clear glass vial with 20 mm dark grey rubber stopper and 20 mm red MT flip-off seal. Each carton contains one 20 mL vial.

Each mL of Treprostinil Injection, 1 mg/mL, contains 1 mg treprostinil (as treprostinil sodium) and the following non-medicinal ingredients: 3 mg metacresol, 6.3 mg sodium citrate dihydrate, 5.3 mg sodium chloride, 0.24 mg sodium hydroxide, and water for injection. Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

Each mL of Treprostinil Injection, 2.5 mg/mL, contains 2.5 mg treprostinil (as treprostinil sodium) and the following non-medicinal ingredients: 3 mg metacresol, 6.3 mg sodium citrate dihydrate, 5.3 mg sodium chloride, 0.32 mg sodium hydroxide, and water for injection. Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

Each mL of Treprostinil Injection, 5 mg/mL, contains 5 mg treprostinil (as treprostinil sodium) and the following non-medicinal ingredients: 3 mg metacresol, 6.3 mg sodium citrate dihydrate, 5.3 mg sodium chloride, 0.62 mg sodium hydroxide, and water for injection. Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

Each mL of Treprostinil Injection, 10 mg/mL, contains 10 mg treprostinil (as treprostinil sodium) and the following non-medicinal ingredients: 3 mg metacresol, 6.3 mg sodium citrate dihydrate, 4 mg sodium chloride, 1.2 mg sodium hydroxide, and water for injection. Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Treprostinil (treprostinil sodium, the soluble sodium salt of treprostinil, is formed during the finished product manufacturing process)

Chemical name:
Acetic acid, [[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3- hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]-monohydrate

[(1*R*,2*R*,3a*S*,9a*S*)-2-Hydroxy-1-((3*S*)-3-hydroxyoctyl)-2,3,3a,4,9,9ahexahydro-1*H* cylopent[*b*]naphthalen-5-yl]oxy] acetate monohydrate.

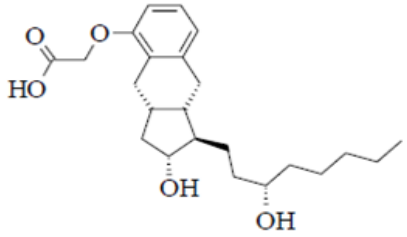
Molecular formula:

Treprostinil: $C_{23}H_{34}O_5$

Molecular mass:

Treprostinil: 390.52 g/mol

Structural formula:



Physicochemical properties:

Description: White to off-white powder

Solubility: Freely soluble in methanol. Aqueous solubility of treprostinil at different pH buffers is summarized below:

Buffer pH	Observation
1.2	Practically insoluble
6.0	Practically insoluble
8.0	Sparingly soluble

pH: 4.01 to 4.07

pKa: 4.5.

Melting point: 123.3°C

Partition coefficient (logP): 4

CLINICAL TRIALS

Study demographics and trial design

Table 6: Summary of Patient Demographics for Study P01:04/05 in Patients with PAH

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
P01:04 and P01:05	12-week, multicenter, randomized, double-blind, parallel studies comparing continuous subcutaneous Treprostinil to placebo	Average 9.3 ng/kg/min continuous subcutaneous injection at 12 weeks	470	45 (9-75) years	81% Female

PAH = Pulmonary Arterial Hypertension

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of treprostinil to placebo in a total of 470 patients with NYHA Class II (11%), III (81%), or IV (7%) pulmonary arterial hypertension (PAH). PAH was idiopathic/heritable in 58% of patients, associated with connective tissue diseases in 19%, and the result of congenital systemic-to-pulmonary shunts in 23%. The mean age was 45 (range 9 to 75 years). About 81% were female and 84% were Caucasian. Pulmonary arterial hypertension had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with subcutaneous treprostinil may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Treprostinil was administered as a subcutaneous infusion, and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses>40 ng/kg/min. Background therapy, determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol.

Study results

Table 7: Results of Study P01:04/05 in Patients with PAH

Primary Endpoint	Treatment Effect (Subcutaneous Treprostinil– Placebo) mean ± SE (meters)	p-value
Six Minute Walk Test NYHA Class III NYHA Class IV	 21.63 ± 7.69 56.41 ± 25.55	 0.0051 0.0278

Clinical Effects: As the two 12-week studies were identical in design and conducted simultaneously, results were analyzed both pooled and individually. Exercise capacity, as measured by the Six-Minute Walk Test, improved significantly in Class II, III, and IV patients

receiving continuous subcutaneous treprostinil plus conventional therapy (N=232) for 12 weeks, with a median increase of 10 meters in this group compared to those receiving conventional therapy plus placebo (N=236) (p=0.0064). Table 7 specifies the improvements in Six-Minute Walk distance at Week 12 for treprostinil patients with NYHA Class III and IV PAH, for which treprostinil is indicated. Improvements, although not statistically significant, were apparent as early as Week 6 of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by the Dyspnea-Fatigue Rating and Borg Scale. Signs and symptoms of PAH also improved, as did the Physical Dimension component of a Quality of Life Scale. Treprostinil was shown to be effective for the treatment of PAH, either primary (PPH), or secondary to the scleroderma spectrum of diseases or associated with congenital systemic-to-pulmonary shunts (repaired or unrepaired), in NYHA Class III and IV patients who did not respond adequately to conventional therapy.

Hemodynamic Effects: As shown previously in Table 3, and the ACTION and CLINICAL PHARMACOLOGY, Pharmacodynamics Section, hemodynamic effects after chronic subcutaneous therapy with treprostinil were generally consistent with the pharmacological effects seen acutely. There were statistically significant increases in CI and SvO_2, and statistically significant decreases in PAPm, RAPm, PVRI, and SVRI in patients treated with treprostinil for 12 weeks compared to patients treated with placebo. Heart rate and SAPm were unchanged. In patients with pulmonary hypertension, elevated RAPm and PAPm, and reduced CO and SvO_2 are predictive of mortality.

Comparative Bioavailability Studies

Study REM01:14 was a randomized, open-label, two-period crossover bioequivalence study comparing intravenous versus subcutaneous administration of treprostinil in healthy adult volunteers. The objective of the study was to demonstrate steady-state bioequivalence.

Subjects were to receive 72 hours of treprostinil infusion (10 ng/kg/min) by both the intravenous and subcutaneous routes for pharmacokinetic comparisons. Steady-state comparisons were made based on extensive plasma sampling between 48 and 72 hours, for each respective route of administration. A total of 55 adult volunteers (60% male, mean age 36.2 years mean body weight was 73.9 kg) received study drug and were included in the safety population for the study. Fifty-one volunteers received at least 24 hours of treprostinil infusion by both routes and were included in the primary pharmacokinetic analyses.

The primary analysis results are shown in Table 8 and Table 9.

Table 8: Summary of Primary Steady State Pharmacokinetic Parameters (n=51)

Parameter	Statistic	IV	SC	Bioequivalence Comparison[1]
AUC_{SS} (hr*ng/mL)	Geom LS Mean	25.67	27.63	**92.9 (89.8, 96.1)**
	Geom Mean	25.69	27.63	
	CV (%)	22.00	16.22	

$Cmax_{SS}$ (ng/mL)	Geom LS Mean	1.47	1.39	**106.0 (99.4, 113.0)**
	Geom Mean	1.47	1.39	
	CV (%)	37.51	16.06	

[1]Point Estimate (90% Confidence Interval)

The 90% confidence intervals for the ratios of adjusted geometric means (IV/SC) are well within the bioequivalence boundaries (confidence intervals between 80% – 125%) for both AUC_{ss} and $C_{max_{ss}}$. Therefore, intravenous and subcutaneous treprostinil are bioequivalent at steady state.

Other pharmacokinetic assessments included $AUC_{0\text{-}96h}$, AUC_{inf}, C_{max}, observed time to maximal plasma concentration (T_{max}), apparent plasma clearance (CL), apparent volume of distribution (V_z), elimination rate constant of the terminal disposition phase (λ_z), and elimination half-life ($T_{1/2}$). As shown in Table 9, these parameters were comparable between the two routes of administration. Of note, the apparent mean elimination half-life following cessation of IV infusion of treprostinil was 4.4 hours compared to 4.6 hours for SC.

Table 9: Summary of Pharmacokinetic Parameters Related to the Full Profile

IV Infusion (N=51)							
Parameter	**Geom. Mean**	**CV (%)**	**Mean**	**SD**	**Median**	**Min**	**Max**
AUC_{inf} (hr*ng/mL)	76.37	16.32	77.38	12.63	76.21	55.85	102.66
$AUC_{0\text{-}96h}$ (hr*ng/mL)	76.25	16.32	77.26	12.61	76.19	55.80	102.61
C_{max} (ng/mL)	1.68	51.57	1.82	0.94	1.62	0.95	6.73
T_{max} (hr)	21.29	74.96	36.39	27.28	51.00	2.00	69.00
λ_z (1/hr)	0.201	51.80	0.238	0.123	0.231	0.030	0.503
$T_{1/2}$ (hr)	3.45	90.21	4.41	3.98	3.00	1.38	23.36
CL (mL/min/kg)	9.43	16.61	9.56	1.59	9.45	7.01	12.89
V_z (L/Kg)	2.82	88.29	3.65	3.22	2.68	0.95	16.76

SC Infusion (N=51)							
Parameter	**Geom. Mean**	**CV (%)**	**Mean**	**SD**	**Median**	**Min**	**Max**
AUC_{inf} (hr*ng/mL)	78.44	15.06	79.31	11.95	80.10	58.94	110.26
$AUC_{0\text{-}96h}$ (hr*ng/mL)	78.34	15.10	79.21	11.96	80.05	58.91	110.22
C_{max} (ng/mL)	1.41	15.70	1.43	0.22	1.45	1.01	1.93
T_{max} (hr)	36.47	46.61	50.27	23.43	63.00	2.00	69.05

λ_z (1/hr)	0.168	37.21	0.182	0.068	0.182	0.039	0.367
$T_{1/2}$ (hr)	4.13	59.04	4.61	2.72	3.82	1.89	18.00
CL (mL/min/kg)	9.18	14.95	9.28	1.39	8.99	6.53	12.22
V_z (L/Kg)	3.28	65.22	3.71	2.42	3.04	1.63	16.54

DETAILED PHARMACOLOGY

Pharmacodynamics

Treprostinil is a tricyclic benzindene analogue of prostacyclin (PGI_2, epoprostenol) with potent systemic and pulmonary vasodilatory and platelet antiaggregatory effects when studied *in vitro* and *in vivo*, and without limiting cardiac effects.

Treprostinil (1-1000 nM) produces concentration-dependent relaxation of isolated rabbit precontracted mesenteric arteries and is approximately 45 times more potent than PGE_2. In anesthetized rats, treprostinil produces dose-dependent decreases in mean arterial blood pressure when administered by the subcutaneous (29-60 mmHg at 25-100 µg/kg/min), or oral (35 and 55 mmHg at 1 and 5 mg/kg) routes, respectively. In anesthetized rats, intravenous treprostinil is approximately 10 times less potent than PGI_2. In anesthetized rabbits, treprostinil and PGI_2 (140 and 200 ng/kg/min, i.v. respectively) decrease mean arterial blood pressure 10 and 16 mmHg, respectively.

In anesthetized closed-chest cats, treprostinil (3-30 µg/kg/min, i.v., 20 min each dose) produces dose-dependent decreases in diastolic blood pressure (22-74 mmHg). Maximum hypotension occurs within 5 minutes and returns to baseline within 40 minutes upon terminating the infusion.

In anesthetized open-chest cats, treprostinil (0.1-3.0 µg/kg/min, i.v. 20 min each dose) produces dose-dependent decreases in mean systemic arterial and mean pulmonary arterial blood pressure with little effect on heart rate. At 0.3 to 3.0 µg/kg/min, treprostinil produces dose-dependent reductions in hypoxia-induced increments in pulmonary arterial blood pressure and pulmonary vascular resistance. Treprostinil is approximately 3 to 10 times less potent than PGI_2 as a vasodilator under hypoxic and normoxic conditions.

In anesthetized newborn piglets, treprostinil (6 and 12 µg/kg, i.v. bolus) abolished hypoxia-induced increases in pulmonary vascular resistance.

In anesthetized dogs, intravenous boluses (0.32-3.2 µg/kg) or infusions (0.1-1.0 µg/kg/min for 10 min) of treprostinil produce dose-dependent decreases in blood pressure. Four-hour intravenous infusions of treprostinil (0.1-3.0 µg/ kg/min) produce dose-dependent decreases in mean systemic arterial and mean pulmonary arterial blood pressures mediated through decreases in vascular resistance in these circulatory beds. The vascular effects of treprostinil are rapid in onset achieving maximum effect within 5-10 minutes with equally rapid recovery upon termination of the infusions.

Treprostinil produces equivalent effects to those of PGI_2 on the systemic and pulmonary vascular beds yet is approximately 10 times less potent than PGI_2. Treprostinil and PGI_2 treatment-related cardiac effects include modest decreases in inotropy and lusitropy and

modest increases in heart rate. ECG changes observed in the dog were inconsistent (occurring predominantly post-infusion) and considered not to be related to treprostinil. The cardiac effects are not major, are not dose dependent, are not sustained throughout treatment, and are interpreted to be generally secondary to the prominent vascular effect and not due to a direct effect on the myocardium. Treprostinil treatment is associated with dose-dependent increases in plasma angiotensin II concentration, which correlate with the decreases in mean arterial blood pressure. Pretreatment of animals with enalapril blocks, digoxin attenuates, and furosemide potentiates the treprostinil treatment-related increases in plasma angiotensin II concentration without significantly affecting the hemodynamic profile of treprostinil.

In conscious dogs, infusions of treprostinil (0.3-3 µg/kg/min, i.v. 10 minutes each) produce dose- related decreases in systolic (18-40 mmHg) and diastolic (13-45 mmHg) arterial blood pressures accompanied by small increases in heart rate (13-30 bpm).

There were no adverse effects of treprostinil in autonomic, respiratory, gastrointestinal, uterine motility, inflammatory, or platelet aggregation secondary pharmacologic evaluations.

Pharmacokinetics

In a series of 13- and 26-week toxicological/toxicokinetic studies in rats and dogs, treprostinil was delivered to the systemic circulation when administered by continuous subcutaneous or intravenous infusion, and relatively linear kinetics were obtained with increasing doses. Linear kinetics were also observed in reproductive studies in rats and rabbits.

In vitro binding of labeled-treprostinil in human plasma was 91.0%, with the compound having no significant effect on the plasma protein binding of digoxin or warfarin.

Tissue distribution studies in rats with tritium or carbon-labeled treprostinil indicated that radioactivity was widely distributed into tissues and was preferentially distributed to organs of the central compartment, including the stomach and intestinal tract.

Metabolic studies in rats and humans indicated that less than 5% of treprostinil was eliminated unchanged. Five metabolites were identified by LC/MS in human urine with no single metabolite exceeding 15% of the dose.

Balance/excretion studies of labeled-treprostinil in rats and dogs showed that the dose was found in the feces (65-80%) and urine (13-26%). In contrast, human volunteers excreted 13.4% and 78.6% of the dose in feces and urine, respectively. The reason for this difference is not known, but biliary excretion/enterohepatic recirculation may be significant in animals.

Treprostinil showed no inhibitory potential toward cytochrome P450 isozymes when tested *in vitro*.

TOXICOLOGY

The preclinical toxicology of treprostinil has been extensively evaluated in a series of *in vitro* and *in vivo* genetic toxicology studies, reproductive toxicology studies in rats and rabbits, and single and repeated dose toxicity studies in mice, rats and dogs.

Acute Toxicity Studies

Treprostinil has low oral and intravenous acute toxicity in mice and rats (Table 10).

Table 10: Incidence of Death in Acute Toxicity Studies

Species	No. per Group	Dose (mg/kg)	Route	MLD mg/kg
Mouse	10 M, 10 F 20 M, 20 F	150, 300 0	oral	150
	10 M, 10 F	0, 100	i.v.	100
Rat	10 M, 10 F 20 M, 20 F	75, 150, 300 0	oral	114 M, 92 F*
	10 M, 10 F 20 M, 20 F	50, 100 0	i.v.	50

MLD = Minimum lethal dose *Median lethal dose

In acute subcutaneous toxicity studies in rats and dogs, the maximum dose that did not produce adverse clinical signs was approximately 400 and 500 ng/kg/min, respectively. In the rat, slight ataxia occurred at approximately 490 ng/kg/min and reversed during the infusion period.

Long-term Toxicity Studies

In repeated dose toxicity studies, treprostinil was well tolerated in rats and dogs when given continuously by subcutaneous infusion for up to 6 months or intravenous infusion for up to 3 months. In dogs, dose-limiting toxicity characterized by gastrointestinal changes (emesis, loose stools, intestinal intussusception, hypoactivity, rectal prolapse) contributing to moribundity and death was observed at doses of ≥300 ng/kg/min. This spectrum of gastrointestinal changes has not been observed in the clinical studies.

In both rats and dogs given treprostinil doses up to 450 ng/kg/min and 200 ng/kg/min, respectively, treprostinil-related toxicity was limited to reversible, dose-related reactions at the infusion site and included lumps, masses/nodules, swellings, erythema and/or intermittent pain (dogs only). Microscopic evaluation demonstrated these areas to have local inflammation (abscess or cellulitis), edema, fibrosis or hemorrhage. Although these changes were also observed in saline control animals, the higher incidence and greater severity in the vehicle control and treated groups suggested that these reactions were related to pump implantation, catheterization technique, and/or irritability of the vehicle that was enhanced when administered in combination with treprostinil.

In rats given treprostinil in repeated dose toxicity studies, other treatment-related findings have included reversible redness of extremities (due to the vasodilatory pharmacological activity of treprostinil) observed at all doses and minimal, reversible increases in mean white blood cell counts, total bilirubin and splenic weights (no histological correlation) observed at 450 ng/kg/min. In dogs, there were minimal, transient and reversible decreases in body weight and

food consumption, and reversible increases in mean white blood cell counts.

Treprostinil diolamine did not demonstrate any carcinogenic effects in mouse or rat carcinogenicity studies. Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors. The exposures obtained at the highest dose levels used in males and females are about 8- and 17-fold, respectively, the human exposure at the mean dose of 3.4 mg BID. Oral administration of treprostinil diolamine to Sprague Dawley rats at 0, 1, 3 and 10 mg/kg/day daily for 104 weeks did not significantly increase the incidence of tumors. The exposures obtained at the highest dose levels used in males and females are about 21- and 29-fold, respectively, the human exposure.

Table 11: Long-term Toxicity Studies - Continuous Subcutaneous (s.c.) or Intravenous (i.v.) Infusion

Species / Strain	No./Sex/ Group	Dose (ng/kg/min)	Duration/ Route	Findings
Rat S-D	7	0*, 0, 17, 67, 200	3 days / s.c.	Treprostinil was non-irritating and well tolerated up to doses of 200 ng/kg/min.
	85	0, 450 50,150	2 weeks / s.c.	Drug-related effect of regenerative anemia with a shift to larger, more immature cells in the low- and mid-dose groups. An inverse relationship of dose to alteration of RBC parameters.
	8	50, 150, 450, 900, 1500	2 weeks / i.v.	Reductions in body weight and food consumption during the first week of the study, and motor activity counts generally at mid to high doses. Effects on various function observational battery parameters more prevalent at the high dose. Decreased platelets, increased mean platelet volume, red cell distribution width, and reticulocyte count, as well as altered electrolytes (sodium, potassium and chloride) at mid to high doses
	10	0, 50, 150, 450	1 month / s.c.	Minor reversible lesions at the infusion site and redness of extremities.

Species / Strain	No./Sex/ Group	Dose (ng/kg/min)	Duration/ Route	Findings
	54	0*, 0, 450 50, 150	3 months / s.c.	Reversible skin lesions, edema, inflammation around pump in all groups. Hematological and clinical chemistry changes were affected by frequent surgical intervention for pump replacement.
	15	50, 300, 900	13 weeks / i.v.	Reduction in platelet count and skin redness at mid and high doses
	15	0*, 0, 50, 150, 450	6 months / s.c.	Treprostinil was generally well tolerated. Slight increases in WBC, total bilirubin, and splenic weights (all reversible) at high dose. Reversible redness of extremities. Lesions, lumps, swellings, and/or thickening of the skin around infusion site - all groups and more frequent at high dose.
Dog, Beagle	1	100, 200 with various buffers)	4 days / s.c.	Decreased appetite and/or diarrhea. Lumps and/or soft swellings at and around infusion site.
	32	0, 600→ 400 50, 200	2 weeks / s.c.	Vomiting and loose stools. Lesions and/or haemorrhage and congestion at infusion site. Two high-dose males had intestinal intussusceptions with one having rectal prolapse.
	2	50, 100, 200, 400	2 weeks i.v.	Soft and/or liquid feces and reductions in body weight gain were seen at all doses, but were most severe at 24 high dose. Reductions in food consumption at mid dose. Effect on platelets and mean platelet volume at higher doses, and jejunal hemorrhage in one high dose animal and associated gross changes in the GI tract of other animals were all considered to be treatment-related

Species / Strain	No./Sex/ Group	Dose (ng/kg/min)	Duration/ Route	Findings
	4	50, 100, 200	13 weeks / i.v.	Soft or liquid feces, red skin on the pinnae, muzzle or lower jaw at the mid and high-dose, reduced body weight and food consumption in high-dose animals, and elevated mean platelet volume in high dose males and mid and high dose females, all of which were reversible following a 4- week recovery period.
	3	0*, 0, 50, 150 →100, 300 → 200	13 weeks / s.c.	Reversible dose-related increase in WBC. Redness of skin and at infusion site. Occasional pain when infusion site palpated. Dark discoloration, masses and/or thickening at and around infusion site, with histological correlation of edema, hemorrhage, fibrosis, and cellulitis in all groups, with less incidence and/or severity in saline control.
	4	0*, 0, 50, 100, 200	6 months / s.c.	Redness of skin. Occasional pain when infusion site palpated. Reversible lumps and/or swellings at/around infusion site with histological findings consisting of cellulitis, edema, fibrosis, and hemorrhage in all groups, with less incidence and/or severity in saline group.

S-D = Sprague-Dawley *Saline.

Mutagenicity

Treprostinil is not mutagenic or clastogenic in in vitro and in vivo genetic toxicological assays (Table 12).

Table 12: *In Vivo* and *In Vitro* Mutagenicity Studies

Study	Species	Dose/Concentration	Findings
Ames Assay	*Salmonella typhimurium*	Up to 5000 mcg/plate with and without S9 metabolic activation	Treprostinil was non-mutagenic at concentrations ≤500 mcg/plate. (Above these concentrations, toxicity of treprostinil toward the bacterial tester strains precluded further evaluation of the results.)
Bacterial Reverse Mutation Assay	*Salmonella typhimurium* *E. coli* WP2 *uvr*A	Up to 5000 mcg/plate with and without S9 metabolic activation	Treprostinil was non-mutagenic at concentrations ≤5000 mcg/plate.
Mouse Lymphoma Forward Mutation Assay	Mouse lymphoma L5178Y cell line	300 and 400 mcg/mL with and without S9 metabolic activation	Treprostinil was negative for inducing forward mutations over a range of concentrations.
Micronucleus Test	Rats Sprague-Dawley	0, 500, 1000,1500 ng/kg/min	Treprostinil was negative in this test.

Reproduction and Teratology

Treprostinil had no effect on adult reproduction, conceptus, early development and growth in rats given up to 450 ng/kg/min by continuous subcutaneous infusion. Administration of treprostinil by continuous subcutaneous infusion during major organogenesis was not teratogenic in pregnant rats at doses up to 900 ng/kg/min (Table 13).

In pregnant rabbits, developmental toxicity characterized by minimal increases in fetal skeletal variations/litter was observed at doses of 150 and 300 ng/kg/min and was associated with maternal toxicity. No developmental toxicity was seen in rabbits at 50 ng/kg/min.

In the Pre- and Postnatal Developmental Study in rats given treprostinil by continuous subcutaneous infusion at doses of 50, 150 or 450 ng/kg/min, the F1 mating index was reduced (not statistically significant) at 450 ng/kg/min. There were no other treatment-related changes in this study and the no observable adverse effect level (NOAEL) for F0 maternal toxicity was 450 ng/kg/min, the conservative NOAEL for F1 male and female reproductive toxicity was 150

ng/kg/min, and the NOAEL for F0 reproductive toxicity and for F1 and F2 developmental toxicity was 450 ng/kg/min.

Table 13: Reproduction and Teratology Studies - Continuous Subcutaneous Infusion

Study	Species/ Strain	No./ Group	Dose (ng/kg/min)	Duration	Findings
Segment I Fertility and General Reproductive Performance	Rat Sprague-Dawley	25 M 25 F	0, 50, 150, 450	M: 10 weeks (pre- breed) and 2 weeks (mating). F: 2 weeks (pre- breed), 2 weeks (mating) and continued until GD Day 6	NOAEL was 50 ng/kg/min for both adult male and female systemic toxicity, and ≥450 ng/kg/min for reproductive and developmental toxicity.
Segment II Teratology	Rat Sprague-Dawley	25 F mated	0, 50, 150, 450, 900	GD 6-20	NOAEL was 150 and ≥900 ng/kg/min for maternal and developmental toxicity, respectively.
	Rabbit New Zealand White	20 F mated	0, 50, 150, 300	GD 6-19	No NOAEL was established for maternal toxicity; and was 50 ng/kg/min for developmental toxicity.
Segment III Peri-postnatal	Rat Sprague-Dawley	25 F mated	0, 50, 150, 450	GD 6-21	NOAEL was 450 ng/kg/min for F0 maternal toxicity; 150 ng/kg/min for F1 offspring; and 450 ng/kg/min for F0 reproductive F1 and F2 developmental toxicity.

GD = Gestational Day

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2. Vachiery, JL., Hill, N., Zwicke, D., Barst, R.J., Blackburn, S., Naeije, R. Transitioning From IV Epoprostenol to Subcutaneous Treprostinil in Pulmonary Arterial Hypertension. Chest 2002;121:1561-1565.

3. REMODULIN® (solution, 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL), control 203551, product monograph, United Therapeutics Corporation. (2017-06-13).

PART III: CONSUMER INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTreprostinil Injection

Read this carefully before you start taking Treprostinil Injection and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Treprostinil Injection.

SERIOUS WARNINGS AND PRECAUTIONS

- **Long term intravenous infusions of Treprostinil Injection are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs), and sepsis (blood infection, fever, headache, fatigue), which may be fatal.**
- Abrupt withdrawal or sudden large reductions in dosage of Treprostinil Injection may result in worsening of pulmonary hypertension symptoms, and should be avoided.
- Treprostinil Injection is approved for subcutaneous (undiluted) or intravenous (diluted) use only.
- In order to reduce the risk of infection, sterile technique must be used in the preparation and administration of Treprostinil Injection.
- Treprostinil Injection should be used only by doctors experienced in the diagnosis and treatment of pulmonary hypertension. Treprostinil Injection therapy must be started by a health professional with equipment for emergency care and monitoring.
- Treprostinil Injection dosage should be increased cautiously in patients with liver or kidney problems.

ABOUT THIS MEDICATION

What is Treprostinil Injection used for?

Treprostinil Injection is approved for the long-term, subcutaneous (under the skin) or intravenous (directly into a vein) treatment of pulmonary arterial hypertension (PAH) in NYHA Class III and IV patients who did not respond adequately to conventional therapy.

How does Treprostinil Injection work?:

Treprostinil causes widening of blood vessels in the lungs and body, and prevents platelets in the blood from sticking together. The effects of these actions may include improvement in some measures of heart function and ability to exercise.

What are the ingredients in Treprostinil Injection?

Medicinal Ingredients: Treprostinil (as treprostinil sodium).
Non-medicinal ingredients: Hydrochloric acid, metacresol %), sodium chloride, sodium citrate dihydrate, sodium hydroxide, and water for injection.

Treprostinil Injection comes in the following dosage forms:

Treprostinil Injection is supplied in 20 mL multi-use vials with 20 mg /20 mL (1 mg/mL), 50 mg /20 mL (2.5 mg/mL), 100 mg /20 mL (5 mg/mL) and 200 mg /20mL (10 mg/mL) of treprostinil. Treprostinil Injection can be used undiluted for subcutaneous use, but must be diluted for intravenous infusion with 0.9% Sodium Chloride Injection or Sterile Water for Injection at concentrations as low as 0.004 mg/mL prior to administration.

Do not use Treprostinil Injection if:

Treprostinil Injection should not be used in patients with known hypersensitivity (allergy) to the active ingredient, any of its non-medicinal ingredients, or to similar compounds.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Treprostinil Injection. Talk about any health conditions or problems you may have, including if you:

- have liver or kidney dysfunction.
- are a pregnant or nursing female.
- are younger than 16, or older than 65 years of age.
- have any allergies to Treprostinil Injection, including treprostinil sodium, hydrochloric acid, metacresol, sodium chloride, sodium citrate, sodium hydroxide or components of the container.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Treprostinil Injection:
The lowering of blood pressure and inhibition of platelet aggregation caused by Treprostinil Injection may be increased by drugs that alter blood pressure (diuretics, antihypertensive agents, vasodilators) or inhibit platelet aggregation (anticoagulants).

PROPER USE OF THIS MEDICATION

How to take Treprostinil Injection:
Therapy with Treprostinil Injection may be used for prolonged periods, and your ability to use Treprostinil

Injection and care for a pump and needles should be carefully considered. Your health professional will decide whether Treprostinil Injection will be given to you subcutaneously or intravenously, and will teach you how to use the pump. They will determine your correct starting dose, and will instruct you when to change your Treprostinil Injection dose.
Treprostinil Injection is given **subcutaneously (under the skin)** by continuous infusion, through a self-inserted catheter (tube), using an infusion pump designed for subcutaneous drug delivery.
Diluted Treprostinil Injection is given **intravenously (into the vein)** by continuous infusion, through a surgically-placed catheter, using an infusion pump designed for intravenous drug delivery.

Usual Dose: Once you begin Treprostinil Injection therapy, your doctor will adjust your infusion rate to establish a dose at which PAH symptoms are improved, while minimizing Treprostinil Injection side effects.

Overdose: If you think that you received too much Treprostinil Injection due to:

- Accidental bolus
- Errors in pump program rate of administration
- Or any other reason

If you think you, or a person you are caring for, have taken too much Treprostinil Injection, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose: Patients must have a second infusion pump and infusion sets available, to avoid potential interruptions of the infusion.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What are possible side effects from using Treprostinil Injection?
These are not all the possible side effects you may feel when taking Treprostinil Injection. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The most common side effects reported with Treprostinil Injection given subcutaneously are infusion site pain and reaction (redness or rash). Other side effects include headache, diarrhea, nausea, rash, jaw pain, vasodilatation, dizziness, edema and hypotension (low blood pressure, fainting), and these are generally considered to be related to the effects of treprostinil, whether given subcutaneously or intravenously. Events potentially related to intravenous delivery include line infections (redness, tenderness, swelling, or pus at infusion site), sepsis (blood infection, fever, headache, fatigue), arm swelling, paresthesia (numbness), hematoma (bruising) and pain. You should contact your health professional about treatment for any side effects you may experience.

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	Infusion site pain	√		
	Infusion site reaction Redness / rash	√		
	Widening of the blood vessels	√		
	Dizziness, swelling	√		
Uncommon	Low blood pressure, fainting		√	
	IV Line Infection (redness, tenderness, swelling, or pus at infusion site)		√	
	Sepsis (blood infection, fever, headache, fatigue)		√	
	Increased bleeding		√	

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Treprostinil Injection should be stored at room temperature at 15°C to 30°C. The products are to be stored in the original carton packaging and protected from light.
Treprostinil Injection vials should be looked at to make sure the vial contents are clear and the vial is not damaged.
A single vial of Treprostinil Injection should be used for no more than 30 days after the initial puncture of the rubber stopper.
During use, a single reservoir (syringe) of undiluted Treprostinil Injection can be administered up to 72 hours at 37°C.
Diluted Treprostinil Injection solution (for intravenous use) can be administered up to 48 hours at 40°C when diluted to concentrations as low as 0.004 mg/mL in 0.9% Sodium Chloride Injection or Sterile Water for Injection.
Inspect the liquid as often as possible to make sure it is clear and free of leaks and particles. If it is hazy, shows particles or leaks, it should be discarded.
Keep out of reach and sight of children.

MORE INFORMATION

If you want more information about Treprostinil Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-products-database.html; Marcan Pharmaceuticals Inc.'s website www.marcanpharma.com, or by calling 1-855-627-2261

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