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NDC 0781-3420-80
Treprostinil Injection
20 mg/20 mL (1 mg/mL)
Rx only 20 mL Multi-dose Vial
SANDOZ a Novartis company

WSB110D3R3
Unitaire 15/20/30ml

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured in Canada by
Sandoz Canada Inc. for
Sandoz Inc.
Princeton, NJ 08540

06-2014M

NDC 0781-3420-80

Treprostinil Injection

20 mg/20 mL

(1 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

Each mL contains:
1 mg Treprostinil
Each mL also contains 6.3 mg sodium citrate, 5.3 mg sodium chloride, 3 mg metacresol.
Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

Prior to intravenous infusion, Treprostinil Injection must be diluted with Sterile 0.9% Sodium Chloride Solution or Water for Injection.

NDC 0781-3420-80

Treprostinil Injection

20 mg/20 mL

(1 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

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128 CODE AREA

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(b) (4)

WSB110D3R3
Unitaire 15/20/30ml

4613226

NDC 0781-3425-80
Treprostinil Injection
50 mg/20 mL (2.5 mg/mL)
Rx only 20 mL Multi-dose Vial
SANDOZ a Novartis company

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured in Canada by
Sandoz Canada Inc. for
Sandoz Inc.
Princeton, NJ 08540

06-2014M

NDC 0781-3425-80

Treprostinil Injection

50 mg/20 mL

(2.5 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

Each mL contains:
2.5 mg Treprostinil
Each mL also contains 6.3 mg sodium citrate, 5.3 mg sodium chloride, 3 mg metacresol.
Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

Prior to intravenous infusion, Treprostinil Injection must be diluted with Sterile 0.9% Sodium Chloride Solution or Water for Injection.

NDC 0781-3425-80

Treprostinil Injection

50 mg/20 mL

(2.5 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

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WSB110D3R3
Unitaire 15/20/30ml

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NDC 0781-3427-80
Treprostinil Injection
100 mg/20 mL (5 mg/mL)
Rx only 20 mL Multi-dose Vial
SANDOZ a Novartis company

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured in Canada by
Sandoz Canada Inc. for
Sandoz Inc.
Princeton, NJ 08540

06-2014M

NDC 0781-3427-80

Treprostinil Injection

100 mg/20 mL

(5 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

Each mL contains:
5 mg Treprostinil
Each mL also contains 6.3 mg sodium citrate, 5.3 mg sodium chloride, 3 mg metacresol.
Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

Prior to intravenous infusion, Treprostinil Injection must be diluted with Sterile 0.9% Sodium Chloride Solution or Water for Injection.

NDC 0781-3427-80

Treprostinil Injection

100 mg/20 mL

(5 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

VARNISH FREE AREA

UPC CODE AREA

N 3 0781-3427-80 3

128 CODE AREA

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BOTTOM

- Varnish
- PMS 541 (Sandoz Blue)
- PMS 362 (Grass)
- PMS 186 (Red)
- PMS 116 (Honey)
- PMS 2915 (Sky)
- PMS 381 (Lime)
- PMS 272 (Purple)
- PMS 137 (Orange)
- Black
- PMS 2905 (Ice)
- PMS 221 (Carmine)
- PMS 321 (Teal)
- PMS 731 (Brown)

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4613228

SANDOZ
a Novartis company

Rx only 20 mL Multi-dose Vial

200 mg/20 mL (10 mg/mL)

Treprostinil Injection

NDC 0781-3430-80

(b) (4)

WSB110D3R3
Unitaire 15/20/30ml

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured in Canada by
Sandoz Canada Inc. for
Sandoz Inc.
Princeton, NJ 08540

06-2014M

NDC 0781-3430-80

Treprostinil Injection

200 mg/20 mL

(10 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

Each mL contains:
10 mg Treprostinil
Each mL also contains 6.3 mg sodium citrate, 4 mg sodium chloride, 3 mg metacresol. Hydrochloric acid and sodium hydroxide may have been added to adjust pH.

Prior to intravenous infusion, Treprostinil Injection must be diluted with Sterile 0.9% Sodium Chloride Solution or Water for Injection.

NDC 0781-3430-80

Treprostinil Injection

200 mg/20 mL

(10 mg/mL)

For Subcutaneous or Intravenous Infusion Only

Sterile

20 mL Multi-dose Vial

Rx only

SANDOZ
a Novartis company

(b) (4)

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SANDOZ

Treprostinil Injection

℞ only

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TREPROSTINIL Injection, for subcutaneous or intravenous use
Initial U.S. Approval May 2002

RECENT MAJOR CHANGES

Dosage and Administration (2.1, 2.5) 12/2014

INDICATIONS AND USAGE

Treprostinil injection is a prostacyclin vasodilator indicated for:
- Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%) (1.1)
- Patients who require transition from Flolan®, to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition. (1.2)

DOSAGE AND ADMINISTRATION

PAH in patients with NYHA Class II-IV symptoms:
- Initial dose for patients new to prostacyclin infusion therapy: 1.25 ng/kg/min increase based on clinical response (increments of 1.25 ng/kg/min per week for the first 4 weeks of treatment, later 2.5 ng/kg/min per week). Avoid abrupt cessation. (2.2, 2.3)
- Mild to moderate hepatic insufficiency: Decrease initial dose to 0.625 ng/kg/min. Severe hepatic insufficiency: No studies performed. (2.4)

Transition from Flolan®:
Increase the treprostinil injection dose gradually as the Flolan dose is decreased, based on constant observation of response. (2.6)

Administration:
Continuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous infusion (dilution required) if subcutaneous infusion is not tolerated. (2.1, 2.5)

DOSAGE FORMS AND STRENGTHS

- Treprostinil injection is supplied in 20 mL vials containing 20, 50, 100, or 200 mg of treprostinil (1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL). (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- For intravenous infusion use an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. (5.1)
- Do not abruptly lower the dose or withdraw dosing. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence >3%) reported in clinical studies with treprostinil injection: subcutaneous infusion site pain and reaction, headache, diarrhea, nausea, jaw pain, vasodilatation, edema, and hypotension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Blood pressure lowering drugs (e.g., diuretics, antihypertensive agents, or vasodilators): Risk of increased reduction in blood pressure (7.1)
- Treprostinil injection inhibits platelet aggregation. Potential for increased risk of bleeding, particularly among patients on anticoagulants. (7.2)
- Treprostinil injection dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (7.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Treprostinil injection is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%) *[see Clinical Studies (14.1)]*.

It may be administered as a continuous subcutaneous infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections (BSIs), continuous intravenous infusion for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted *[see Warnings and Precautions (5.1)]*.

1.2 Pulmonary Arterial Hypertension in Patients Requiring Transition from Flolan®

In patients with pulmonary arterial hypertension requiring transition from Flolan (epoprostenol sodium), treprostinil injection is indicated to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

2 DOSAGE AND ADMINISTRATION

2.1 General

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. See below for storage and administration time limits for the different diluents.

Table 1. Selection of Diluent

Route	Diluent	Storage limits	Administration limits
SC	None	See section 16	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

2.2 Initial Dose for Patients New to Prostacyclin Infusion Therapy

Treprostinil injection is indicated for subcutaneous (SC) or intravenous (IV) use only as a continuous 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.

2.3 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 adjustments may be undertaken more often if tolerated. Avoid abrupt cessation of infusion *[see Warnings and Precautions (5.4)]*. Restarting a treprostinil injection 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 injection to be re-titrated.

2.4 Patients with Hepatic Insufficiency

In patients with mild or moderate hepatic insufficiency, decrease the initial dose of treprostinil injection to 0.625 ng/kg/min ideal body weight. Treprostinil injection has not been studied in patients with severe hepatic insufficiency *[see Warnings and Precautions (5.3), Use In Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

2.5 Administration

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 treprostinil injection.

Subcutaneous Infusion

Treprostinil injection is administered subcutaneously by continuous infusion without further dilution, via a 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. The ambulatory infusion pump used to administer treprostinil injection should: (1) be small and lightweight, (2) be adjustable to 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.

Treprostinil injection is administered subcutaneously by continuous infusion at a calculated subcutaneous infusion rate (mL/hr) based on a patient's 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:

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

* *Conversion factor of 0.00006 = 60 min/hour × 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, the infusion rate would be calculated as follows:

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

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

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

Intravenous Infusion

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 ambulatory infusion pump used to administer treprostinil injection should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of ±6% or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion sets with an in-line 0.22 or 0.2 micron pore size filter should be used.

Diluted treprostinil injection has been shown to be stable at ambient temperature for up to 48 hours at concentrations as low as 0.004 mg/mL (4,000 ng/mL).

Select the intravenous infusion rate to allow for a desired infusion period length of up to 48 hours between system changeovers. 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:

Step 1

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

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

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

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

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

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

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

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.

2.6 Patients Requiring Transition from Flolan

Transition from Flolan to treprostinil injection is accomplished by initiating the infusion of treprostinil injection and increasing it, while simultaneously reducing the dose of intravenous Flolan. The transition to treprostinil injection should take place in a hospital with constant observation of response (e.g., walk distance and signs and symptoms of disease progression). Initiate treprostinil injection at a recommended dose of 10% of the current Flolan dose, and then escalate as the Flolan dose is decreased (see Table 2 for recommended dose titrations).

Patients are individually titrated to a dose that allows transition from Flolan therapy to treprostinil injection while balancing prostacyclin-limiting adverse events. Increases in the patient's symptoms of PAH should be first treated with increases in the dose of treprostinil injection. Side effects normally associated with prostacyclin and prostacyclin analogs are to be first treated by decreasing the dose of Flolan.

Table 2: Recommended Transition Dose Changes

Step	Flolan Dose	Treprostinil Injection Dose
1	Unchanged	10% Starting Flolan Dose
2	80% Starting Flolan Dose	30% Starting Flolan Dose
3	60% Starting Flolan Dose	50% Starting Flolan Dose
4	40% Starting Flolan Dose	70% Starting Flolan Dose
5	20% Starting Flolan Dose	90% Starting Flolan Dose
6	5% Starting Flolan Dose	110% Starting Flolan Dose
7	0	110% Starting Flolan Dose + additional 5-10% increments as needed

3 DOSAGE FORMS AND STRENGTHS

20-mL vial containing 20 mg treprostinil (1 mg per mL).
20-mL vial containing 50 mg treprostinil (2.5 mg per mL).
20-mL vial containing 100 mg treprostinil (5 mg per mL).
20-mL vial containing 200 mg treprostinil (10 mg per mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Catheter-Related Bloodstream Infection

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.

In an open-label study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about 1 BSI event per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use.

5.2 Worsening PAH upon Abrupt Withdrawal or Sudden Large Dose Reduction

Avoid abrupt withdrawal or sudden large reductions in dosage of treprostinil injection, which may result in worsening of PAH symptoms.

5.3 Patients with Hepatic or Renal Insufficiency

Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function *[see Dosage and Administration (2.4, 2.5), Use In Specific Populations (8.6, 8.7), and Clinical Pharmacology (12.3)]*.

5.4 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) decreases exposure to treprostinil *[see Drug Interactions (7.5)* and *Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling: Infections associated with intravenous administration *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trials Experience

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

Adverse Events with Subcutaneously Administered Treprostinil Injection

Patients receiving treprostinil injection as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of treprostinil injection, infusion site pain and reaction were the most common adverse events among those treated with treprostinil injection. 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. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Table 3: Percentages of subjects reporting subcutaneous infusion site adverse events

	Reaction		Pain	
	Placebo	Treprostinil Injection	Placebo	Treprostinil Injection
Severe	1	38	2	39
Requiring narcotics*	NA†	NA†	1	32
Leading to discontinuation	0	3	0	7

* based on prescriptions for narcotics, not actual use
† medications used to treat infusion site pain were not distinguished from those used to treat site reactions

(Continued)

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of treprostinil injection, whether administered subcutaneously or intravenously.

Adverse Reactions during Chronic Dosing

Table 4 lists adverse reactions defined by a rate of at least 3% more frequent in patients treated with subcutaneous treprostinil injection than with placebo in controlled trials in PAH.

Table 4: Adverse Reactions in Controlled 12-Week Studies of Subcutaneous Treprostinil Injection and at least 3% more frequent than on Placebo

Adverse Reaction	Treprostinil Injection (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Edema	9	3

Reported adverse reactions (at least 3% more frequent on drug than on placebo) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

While hypotension occurred in both groups, the event was experienced twice as frequently in the treprostinil injection group as compared to the placebo group (4% in treprostinil injection treatment group verses 2% in placebo-controlled group). As a potent vasodilator, hypotension is possible with the administration of treprostinil injection. The safety of treprostinil injection was also studied in a long-term, open-label extension study in which 860 patients were dosed for a mean duration of 1.6 years, with a maximum exposure of 4.6 years. Twenty-nine (29%) percent achieved a dose of at least 40 ng/kg/min (max: 290 ng/kg/min). The safety profile during this chronic dosing study was similar to that observed in the 12-week placebo controlled study except for the following suspected adverse drug reactions (occurring in at least 3% of patients): anorexia, vomiting, infusion site infection, asthenia, and abdominal pain.

Adverse Events Attributable to the Drug Delivery System

In controlled studies of treprostinil injection 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 injection, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 treprostinil injection, 4 placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess treprostinil injection (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). 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 *[see Warnings and Precautions (5.1)]*.

6.2 Post-Marketing Experience

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of treprostinil injection. 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 injection. These events are thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia, bone pain, pruritus and dizziness. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

7 DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have been conducted with treprostinil administered subcutaneously (treprostinil injection) and orally (treprostinil diethanolamine).

Pharmacodynamics

7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of treprostinil injection with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

7.2 Anticoagulants

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics

7.3 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

7.4 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

7.5 Effect of Treprostinil on Cytochrome P450 Enzymes

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A. Thus treprostinil injection is not expected to alter the pharmacokinetics of compounds metabolized by CYP enzymes.

7.6 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 *[see Warnings and Precautions (5.4)]*.

Treprostinil injection has not been studied in conjunction with Flolan or Tracleer® (bosentan).

7.7 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

In pregnant rats, continuous subcutaneous infusions of treprostinil during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m^2 basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m^2 basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Animal reproduction studies are not always predictive of human response.

8.2 Labor and Delivery

No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Many drugs are excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of treprostinil injection did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients.

8.5 Geriatric Use

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

8.6 Patients with Hepatic Insufficiency

Treprostinil injection clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, decrease the initial dose of treprostinil injection to 0.625 ng/kg/min ideal body weight, and monitor closely. Treprostinil injection has not been studied in patients with severe hepatic insufficiency *[see Dosage and Administration (2.4), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Insufficiency

No studies have been performed in patients with renal insufficiency. No specific advice about dosing in such patients can be given. *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Signs and symptoms of overdose with treprostinil injection 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 injection.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of treprostinil injection, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of treprostinil injection produce an event of substantial hemodynamic concern (hypotension, near-syncope).

One pediatric patient was accidentally administered 7.5 mg of treprostinil injection 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.

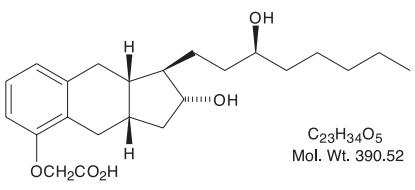
11 DESCRIPTION

Treprostinil injection is a sterile solution of treprostinil formulated for subcutaneous or intravenous administration. Treprostinil injection is supplied in 20 mL multidose vials in four strengths, containing 20 mg, 50 mg, 100 mg, or 200 mg (1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL) of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.52 and a molecular formula of $C_{23}H_{34}O_5$.

The structural formula of treprostinil is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Treprostinil produces vasodilation and tachycardia. Single doses of treprostinil up to 84 mcg by inhalation produce modest and short-lasting effects on QTc, but this is apt to be an artifact of the rapidly changing heart rate. Treprostinil administered by the subcutaneous or intravenous routes has the potential to generate concentrations many-fold greater than those generated via the inhaled route; the effect on the QTc interval when treprostinil is administered parenterally has not been established.

12.3 Pharmacokinetics

The pharmacokinetics of continuous subcutaneous treprostinil injection are linear over the dose range of 1.25 to 125 ng/kg/min (corresponding to plasma concentrations of about 15 pg/mL to 18,250 pg/mL) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 125 ng/kg/min has not been studied.

Subcutaneous and intravenous administration of treprostinil injection demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.

Absorption

Treprostinil injection is relatively 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 2,000 pg/mL.

Distribution

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

Metabolism and Excretion

Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. In a study conducted in healthy volunteers using [^{14}C] treprostinil, 78.6% and 13.4% of the subcutaneous dose was recovered in the urine and feces, respectively, over 10 days. Only 4% was excreted as unchanged treprostinil in the urine. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% and representing 64.4% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide). The identified metabolites do not appear to have activity.

The elimination of treprostinil (following subcutaneous administration) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two compartment model. Systemic clearance is approximately 30 L/hr for a 70 kg person.

Based on in vitro studies treprostinil does not inhibit or induce major CYP enzymes *[see Drug Interactions (7.5)]*.

Special Populations

Hepatic Insufficiency

In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, treprostinil injection at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a C_{max} that was 2-fold and 4-fold, respectively, and an $AUC_{0-\infty}$ that was 3-fold and 5-fold, respectively, values observed in healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

Renal Insufficiency

No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

14 CLINICAL STUDIES

14.1 Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of treprostinil injection 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 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 treprostinil injection 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 injection was administered as a subcutaneous infusion, described in Section 2, DOSAGE AND ADMINISTRATION, 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. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

Hemodynamic Effects

As shown in Table 5, chronic therapy with treprostinil injection resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

Table 5: Hemodynamics during Chronic Administration of Treprostinil Injection in Patients with PAH in 12-Week Studies

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Treprostinil Injection (N=204-231)	Placebo (N=215-235)	Treprostinil Injection (N=163-199)	Placebo (N=182-215)
CI (L/min/m^2)	2.4 ± 0.88	2.2 ± 0.74	+0.12 ± 0.58*	-0.06 ± 0.55
PAPm (mmHg)	62 ± 17.6	60 ± 14.8	-2.3 ± 7.3*	+0.7 ± 8.5
RAPm (mmHg)	10 ± 5.7	10 ± 5.9	-0.5 ± 5.0*	+1.4 ± 4.8
PVRI (mmHg/L/min/m^2)	26 ± 13	25 ± 13	-3.5 ± 8.2*	+1.2 ± 7.9
SVRI (mmHg/L/min/m^2)	38 ± 15	39 ± 15	-3.5 ± 12*	-0.80 ± 12
SvO_2 (%)	62 ± 100	60 ± 11	+2.0 ± 10*	-1.4 ± 8.8
SAPm (mmHg)	90 ± 14	91 ± 14	-1.7 ± 12	-1.0 ± 13
HR (bpm)	82 ± 13	82 ± 15	-0.5 ± 11	-0.8 ± 11

CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance indexed; RAPm = mean right atrial pressure; SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO2 = mixed venous oxygen saturation; HR = heart rate.

* Denotes statistically significant difference between treprostinil injection and placebo, p<0.05.

Clinical Effects

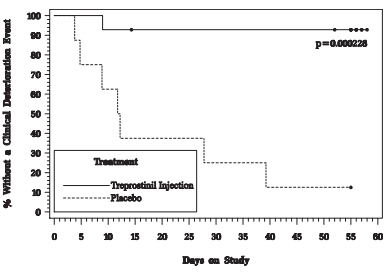
The effect of treprostinil injection on 6-minute walk, the primary end point of the 12-week studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on treprostinil injection was 10 meters and the median change from baseline on placebo was 0 meters from a baseline of approximately 345 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by treprostinil injection during the 6-minute walk, and treprostinil injection also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Treprostinil injection also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

14.2 Flolan-To-Treprostinil Injection Transition Study

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study, patients on stable doses of Flolan were randomly withdrawn from Flolan to placebo or treprostinil injection. Fourteen treprostinil injection and 8 placebo patients completed the study. The primary endpoint of the study was the time to clinical deterioration, defined as either an increase in Flolan dose, hospitalization due to PAH, or death. No patients died during the study.

During the study period, treprostinil injection effectively prevented clinical deterioration in patients transitioning from Flolan therapy compared to placebo (Figure 1). Thirteen of 14 patients in the treprostinil injection arm were able to transition from Flolan successfully, compared to only 1 of 8 patients in the placebo arm (p=0.0002).

Figure 1: Time to Clinical Deterioration for PAH Patients Transitioned from Flolan to Treprostinil Injection or Placebo in an 8-Week Study



16 HOW SUPPLIED/STORAGE AND HANDLING

Treprostinil injection is supplied in 20 mL multidose vials as sterile solutions in water for injection, individually packaged in cartons. Unopened vials of treprostinil injection are stable until the date indicated when stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

A single vial of treprostinil injection should be used for no more than 30 days after the initial introduction into the vial.

Treprostinil injection is supplied as:

Treprostinil Injection	Concentration	Carton of 1 NDC
20 mg/20 mL	1 mg/mL	NDC 0781-3420-80
50 mg/20 mL	2.5 mg/mL	NDC 0781-3425-80
100 mg/20 mL	5 mg/mL	NDC 0781-3427-80
200 mg/20 mL	10 mg/mL	NDC 0781-3430-80

17 PATIENT COUNSELING INFORMATION

Patients receiving treprostinil injection should be given the following information: treprostinil injection is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Patients receiving intravenous infusion should use an infusion set with an in-line filter. Therapy with treprostinil injection will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump 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. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy, Flolan® (epoprostenol sodium).

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