

הודעה על החמרה (מידע בטיחות)

תאריך: __ במרס 2012

שם תכשיר באנגלית: REMODULIN INJECTION 1, 2.5, 5, 10 MG/ML

מספר רישום: 1265930564, 1265730563, 1265630562, 1355531251

שם בעל הרישום: מעבדות רפא בע"מ

השינויים בעלון מסומנים בצבע: צהוב=הוספה, ירוק=יזק, כחול=שינוי מקום.

בעלון לרופא

| פרק בעלון | טקסט נוכחי | טקסט חדש |
|---------------------------|--|--|
| Dosage and Administration | <p>Remodulin is supplied in 20 mL vials in concentrations (1 mg/mL, 2.5 mg/mL, 5 mg/mL) Remodulin can be administered as supplied or diluted for intravenous infusion with Sterile Water for Injection, 0.9% Sodium Chloride Injection prior to administration.</p> <p>Initial Dose</p> <p>Remodulin is administered by continuous infusion. Remodulin 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, the infusion rate should be reduced to 0.625 ng/kg/min.</p> <p>Dosage Adjustments</p> <p>The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).</p> <p>The infusion rate should be increased in increments of no more than 1.25 ng/kg/min</p> | <p>2.1 General</p> <p>Remodulin is supplied in 20 mL vials in concentrations containing 20, 50, 100, or 200 mg of treprostinil (1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL). Remodulin can be administered as supplied or diluted for intravenous infusion with Sterile Water for Injection, 0.9% Sodium Chloride Injection, or Flolan[®]-Sterile Diluent for Injection prior to administration.</p> <p>2.2 Initial Dose for Patients New to Prostacyclin Infusion Therapy</p> <p>Remodulin is administered by indicated for subcutaneous (SC) or intravenous (IV) use only as a continuous infusion. Remodulin 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, the infusion rate should be reduced to 0.625 ng/kg/min.</p> <p>2.3 Dosage Adjustments</p> <p>The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).</p> <p>The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks of treatment and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion,</p> |

depending on clinical response. Dosage adjustments may be undertaken more often if tolerated. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided [see Warnings and Precautions (5.4)]. Restarting a Remodulin 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 Remodulin to be re-titrated.

2.4 Patients with Hepatic Insufficiency

In patients with mild or moderate hepatic insufficiency, the initial dose of Remodulin should be decreased to 0.625 ng/kg/min ideal body weight and should be increased cautiously. Remodulin has not been studied in patients with severe hepatic insufficiency [see Warnings and Precautions (5.5), Use In Specific Populations (8.6) and Clinical Pharmacology (12.3)].

2.5 Patients with Renal Insufficiency

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

2.6 Administration

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

ng/kg/min per week for the first four weeks of treatment and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (See Precautions).

Administration

Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion, 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. The ambulatory infusion pump used to administer Remodulin 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 $\pm 6\%$ or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

For subcutaneous infusion, Remodulin 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 Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. The Subcutaneous Infusion rate is calculated using the following formula:

$$\begin{array}{l} \text{Subcutaneous} \\ \text{Infusion Rate} \\ \text{(mL/hr)} \end{array} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006^*}{\text{Remodulin Vial Strength (mg/mL)}}$$

*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 Remodulin Vial Strength, the infusion rate would be calculated as follows:

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

Example 2:

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

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

Intravenous Infusion

Remodulin must be diluted with either Sterile Water for Injection, or 0.9% Sodium Chloride Injection, or Flolan® Sterile Diluent for Injection and 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 Remodulin. 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

Intravenous Infusion

Remodulin must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection, and is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. 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 Remodulin should: (1) be small and lightweight, (2) have occlusion/no

access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin 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.

Diluted Remodulin 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).

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 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 Remodulin Concentration (mg/mL) can be calculated using the following formula:

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.

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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 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 Remodulin Concentration (mg/mL) can be calculated using the following formula:

Step 1

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

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

Step 2

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

The calculated amount of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent (Sterile Water for Injection, or 0.9% Sodium Chloride Injection, or Flolan®-Sterile Diluent for Injection) to achieve the desired total volume in the reservoir.

The calculated amount of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent (Sterile Water for Injection or 0.9% Sodium Chloride Injection) 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 Remodulin Solution Concentration would be calculated as follows:

Step 1

$$\begin{array}{l} \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{5 \text{ ng/kg/min} \times 60 \text{ kg} \times 0.00006}{1 \text{ mL/hr}} = \begin{array}{l} \mathbf{0.018} \\ \text{mg/mL} \\ \text{(18,000} \\ \text{ng/mL)} \end{array}$$

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

Step 2

$$\begin{array}{l} \text{Amount of} \\ \text{Remodulin Injection} \\ \text{(mL)} \end{array} = \frac{0.018 \text{ mg/mL}}{1 \text{ mg/mL}} \times 50 \text{ mL} = \mathbf{0.9 \text{ mL}}$$

The Diluted Intravenous Remodulin Concentration for the person in Example 3 would thus be prepared by adding 0.9 mL of 1 mg/mL Remodulin 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 Remodulin Solution Concentration would be calculated as follows:

Step 1

$$\begin{array}{l} \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{30 \text{ ng/kg/min} \times 75 \text{ kg} \times 0.00006}{2 \text{ mL/hr}} = \begin{array}{l} \mathbf{0.0675 \text{ mg/mL}} \\ \text{(67,500 ng/mL)} \end{array}$$

The Amount of Remodulin Injection (using 2.5 mg/mL Vial Strength) needed for a total Diluted Remodulin Concentration of 0.0675 mg/mL and a total volume of 100 mL would be calculated as follows:

Step 2

$$\begin{array}{l} \text{Amount of} \\ \text{Remodulin Injection} \\ \text{(mL)} \end{array} = \frac{0.0675 \text{ mg/mL}}{2.5 \text{ mg/mL}} \times 100 \text{ mL} = \mathbf{2.7 \text{ mL}}$$

The Diluted Intravenous Remodulin Concentration for the person in Example 4 would thus be prepared by adding 2.7 mL of 2.5 mg/mL Remodulin 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.

2.7 Patients Requiring Transition from Flolan

Transition from Flolan to Remodulin is accomplished by initiating the infusion of Remodulin and increasing it, while simultaneously reducing the dose of intravenous Flolan. The transition to Remodulin should take place in a hospital with constant observation of response (e.g., walk distance and signs and symptoms of disease progression). During the transition, Remodulin is initiated at a recommended dose of 10% of the current Flolan dose, and then escalated as the Flolan dose is decreased (see Table 1 for recommended dose titrations).

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

Table 1: Recommended Transition Dose Changes

| Step | Flolan Dose | Remodulin 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 |

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).

Dosage Forms and Strengths

Warnings and precautions

Remodulin is indicated for subcutaneous or intravenous use only.

PRECAUTIONS

5.1 Risks Attributable to the Drug Delivery System

Chronic intravenous infusions of Remodulin 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 General Conditions of Use

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Therapy with Remodulin may be used for prolonged periods, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered.

5.3 Dose Modification

Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms [see Dosage and Administration (2)].

5.4 Abrupt Withdrawal or Sudden Large Dose Reduction

Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

Information for Patients

Patients receiving Remodulin should be given the following information: Remodulin is

Remodulin is indicated for subcutaneous or intravenous use only.

PRECAUTIONS

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Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms [see Dosage and Administration).

Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

Information for Patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Therapy with Remodulin 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

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Drug Interactions

Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications.

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

Effect of Other Drugs on Remodulin

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Effect of Remodulin on Other Drugs

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Warfarin - Remodulin 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

Remodulin. 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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In vivo studies: Warfarin - Remodulin does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy

mg dose of warfarin were unaffected by continuous subcutaneous Remodulin at an infusion rate of 10 ng/kg/min.

[Drug Interactions have been moved to a new section 7.]

5.5 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)].

Caution should be used in patients with hepatic or renal impairment (see Special Populations).

5.6 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness [see Drug Interactions (7.5) and Clinical Pharmacology (12.3)].

subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous Remodulin at an infusion rate of 10 ng/kg/min.

Hepatic or Renal Insufficiency

Caution should be used in patients with hepatic or renal impairment (see Special Populations).

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 Remodulin

Patients receiving Remodulin as a

Patients receiving Remodulin 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 Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. 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

Adverse Reactions

| | | |
|---|---|--|
| <p>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 Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. 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.</p> | <p>sometimes severe and could lead to discontinuation of treatment.</p> | |
| <p>Adverse Events Attributable to the Drug Delivery System</p> <p>In controlled studies of Remodulin 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% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 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 Remodulin (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)].</p> <p>There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38)</p> | <p>Adverse Events Attributable to the Drug Delivery System</p> <p>In controlled studies of Remodulin 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% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 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 Remodulin (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.</p> <p>There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38) treated for 12-weeks in an</p> | |

treated for 12 weeks in an open-label study, 2 patients had either line infections or sepsis. Other events potentially related to the mode of infusion include arm swelling, paresthesias, hematoma and pain.

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 Remodulin. 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 due to a combination of their seriousness, frequency of reporting, and potential connection to Remodulin. These events are thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia and bone pain. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

open-label study, 2 patients had either line infections or sepsis. Other events potentially related to the mode of infusion include arm swelling, paresthesias, hematoma and pain.

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

See above in Warnings and Precautions

Drug Interactions

Pharmacodynamics

7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of Remodulin 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 Remodulin 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* (5.6)].

Remodulin 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.

8.1 Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil sodium 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. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

No treprostinil sodium 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.

Pregnancy

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Use in Specific Populations

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin 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.

8.5 Geriatric Use

Clinical studies of Remodulin 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

Remodulin clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight, and monitor closely. Remodulin has not been studied in patients with severe hepatic insufficiency [see Dosage and Administration (2.4), Warnings and Precautions (5.5) 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 patients with renal impairment can be given. [see Clinical Pharmacology (12.3)].

Labor and Delivery

No treprostinil sodium 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.

Nursing Mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

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Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin 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.

Geriatric Use

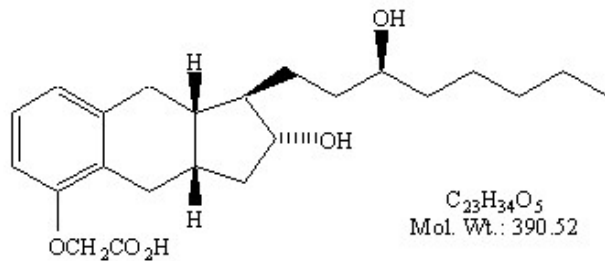
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Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting

Overdose

| | | |
|--|---|---------------------------|
| <p>effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.</p> <p>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 Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).</p> <p>One pediatric patient was accidentally administered 7.5 mg of Remodulin 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.</p> | <p>pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.</p> <p>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 Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).</p> | |
| <p>Remodulin (treprostinil sodium) Injection is a sterile sodium salt solution of treprostinil formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use multidose vials in three 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), 3.0 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.</p> <p>Treprostinil is chemically stable at room temperature and neutral pH.</p> <p>Treprostinil sodium 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 monosodium salt. Treprostinil has a molecular weight of 390.52 412.49 and a molecular formula of C₂₃H₃₄O₅ C₂₃H₃₄NaO₅.</p> <p>The structural formula of treprostinil sodium</p> | <p>Remodulin (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in three strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL Each mL also contains 5.3 mg sodium chloride 3.0 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.</p> <p>Treprostinil is chemically stable at room temperature and neutral pH.</p> <p>Treprostinil sodium 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 monosodium salt. Treprostinil has a molecular weight of 412.49 and a molecular formula of C₂₃H₃₄NaO₅.</p> | <p>Description</p> |

| | | |
|---|---|-------------------------------------|
| is: | The structural formula of treprostinil sodium is: | |
| <div data-bbox="507 309 1114 568" data-label="Chemical-Block">  <p style="text-align: center;"> $C_{23}H_{34}O_5$ Mol. Wt.: 390.52 </p> </div> | | |
| <p>12.1 Mechanism of Action</p> <p>General: The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.</p> <p>12.2 Pharmacodynamics</p> <p>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.</p> <p>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.</p> <p>12.3 Pharmacokinetics</p> <p>The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 22.5 125 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 mcg/mL 15 pg/mL to 18,250 pg/mL) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 22.5 125 ng/kg/min has not been studied.</p> | <p>General: The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.</p> <p>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.</p> <p>Pharmacokinetics</p> <p>The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 22.5 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 mcg/mL and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 22.5 ng/kg/min has not been studied.</p> <p>Subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.</p> <p>Absorption:</p> <p>Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability</p> | <p>Clinical Pharmacology</p> |

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

Absorption:

Remodulin 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 mcg/mL, 2,000 pg/mL.

Distribution:

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

Metabolism: and Excretion

Remodulin (Treprostinil) is substantially metabolized by the liver, but the precise enzymes responsible are unknown, primarily by CYP2C8. In a study conducted in healthy volunteers using [¹⁴C] 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 have been described (HU1 through HU5) were detected in the urine, ranging from 10.2% to 15.5% and representing 64.4% of the dose administered. 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). Four of the metabolites are products of oxidation of the 3-hydroxyoctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide). The identified metabolites do not appear to have activity.

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Based on the results of *in vitro* human hepatic cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether Remodulin induces these enzymes has not been studied.

Excretion: The elimination of Remodulin 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

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.

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Special Populations

Hepatic Insufficiency:

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

In patients with mild or moderate hepatic insufficiency, the initial dose of Remodulin should be decreased to 0.625 ng/kg/min ideal body weight and should be increased cautiously. Remodulin has not been studied in patients with severe hepatic insufficiency.

Renal Insufficiency:

clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

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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.

Effect of Other Drugs on Remodulin:

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen,

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Effect of Other Drugs on Remodulin: In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen – Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

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14.1 Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of Remodulin to placebo in a total of 470 patients with NYHA Class II-IV (11%), III (81%), or IV (7%) pulmonary arterial hypertension (PAH). PAH was primary idiopathic/heritable in 58% of patients, associated with collagen vascular connective tissue diseases in 19%, and the result of congenital systemic-to-pulmonary left to right 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 Remodulin 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. Remodulin was administered as a subcutaneous infusion, described in Section 2, DOSAGE AND ADMINISTRATION, and

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Clinical Studies

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 4, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

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Hemodynamic Effects

As shown in Table 1, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

Table 4: Hemodynamics during Chronic Administration of Remodulin in Patients with PAH in 12-Week Studies

| Hemodynamic Parameter | Baseline | | Mean change from baseline at Week 12 | |
|-----------------------------------|-----------------------|---------------------|--------------------------------------|---------------------|
| | Remodulin (N=204-231) | Placebo (N=215-235) | Remodulin (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 |

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

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.

Clinical Effects

The effect of Remodulin 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 Remodulin 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 Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Remodulin 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.

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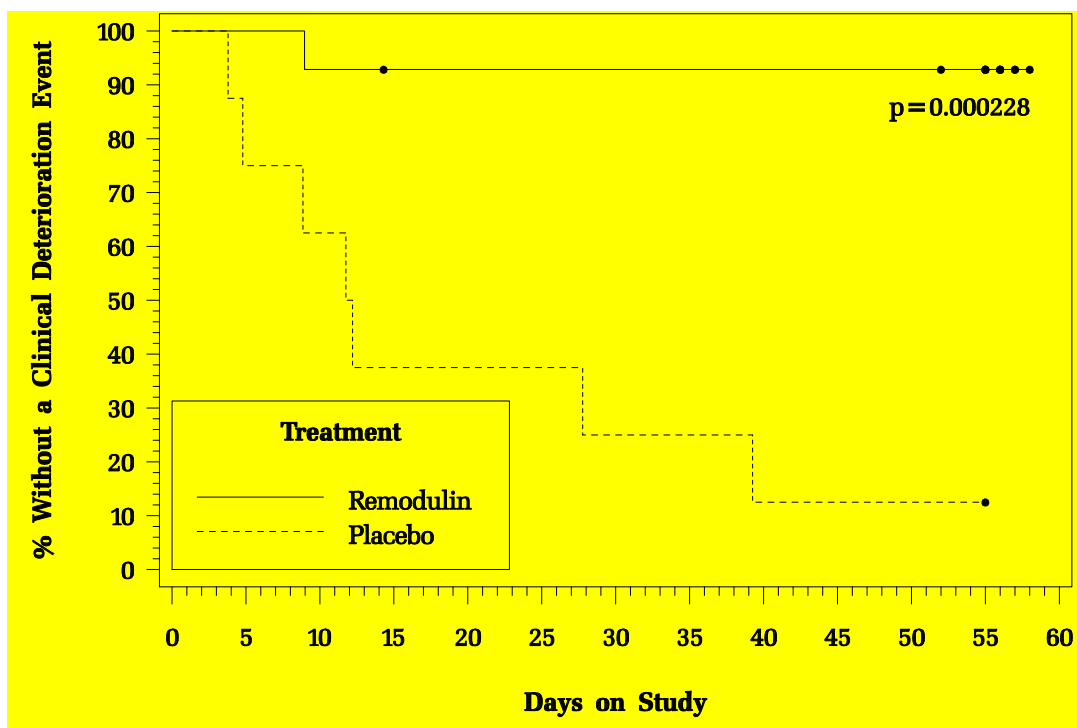
14.2 Flolan-To-Remodulin Transition Study

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

assignment resulting from infusion site symptoms.

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



Remodulin is supplied in 20 mL multi-use multidose vials containing 20, 50, 100, or 200 mg of treprostinil at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL

Remodulin is supplied in 20 mL multi-use vials at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL treprostinil, as sterile solutions in

How supplied/Storage and handling

treprostinil, respectively, as sterile solutions in water for injection, individually packaged in cartons. Each mL contains treprostinil sodium equivalent to 1 mg/mL, 2.5 mg/mL, 5 mg/mL treprostinil. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F). Store at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. Diluted Remodulin Solution can be administered up to 48 hours at 37°C when diluted to concentrations as low as 0.004 mg/mL in Sterile Water for Injection, 0.9% Sodium Chloride Injection, or Flolan® Sterile Diluent for Injection. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

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

20-mL vial containing 20 mg treprostinil sodium equivalent to (1 mg treprostinil per mL), carton of 1 (NDC 66302-101-01).

20-mL vial containing 50 mg treprostinil sodium equivalent to (2.5 mg treprostinil per mL), carton of 1 (NDC 66302-102-01).

20-mL vial containing 100 mg treprostinil sodium equivalent to (5 mg treprostinil per mL), carton of 1 (NDC 66302-105-01).

20-mL vial containing 200 mg treprostinil sodium equivalent to (10 mg treprostinil per mL), carton of 1 (NDC 66302-110-01).

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20-mL vial containing 50 mg treprostinil sodium equivalent to 2.5 mg treprostinil per mL, carton of 1 (NDC 66302-102-01).

20-mL vial containing 100 mg treprostinil sodium equivalent to 5 mg treprostinil per mL, carton of 1 (NDC 66302-105-01).

20-mL vial containing 200 mg treprostinil sodium equivalent to 10 mg treprostinil per mL, carton of 1 (NDC 66302-110-01).

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Therapy with Remodulin 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 Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy, Flolan® (epoprostenol sodium).

**Patient
Counseling
Information**

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