

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

REMODULIN® (treprostinil) Injection, for subcutaneous or intravenous use

Initial U.S. Approval: May 2002

INDICATIONS AND USAGE

Remodulin 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 Remodulin 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 (IV) infusion (dilution required) if subcutaneous infusion is not tolerated. (2.1, 2.5)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None

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)
- Remodulin may cause symptomatic hypotension. (5.4)
- Remodulin inhibits platelet aggregation and increases the risk of bleeding. (5.5)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Pulmonary Arterial Hypertension
- 1.2 Pulmonary Arterial Hypertension in Patients Requiring Transition from Flolan®

2 DOSAGE AND ADMINISTRATION

- 2.1 General
- 2.2 Initial Dose for Patients New to Prostacyclin Infusion Therapy
- 2.3 Dosage Adjustments
- 2.4 Patients with Hepatic Insufficiency
- 2.5 Administration
- 2.6 Patients Requiring Transition from Flolan

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Risk of Catheter-Related Bloodstream Infection
- 5.2 Worsening PAH upon Abrupt Withdrawal or Sudden Large Dose Reduction
- 5.3 Patients with Hepatic or Renal Insufficiency
- 5.4 Risk of Symptomatic Hypotension
- 5.5 Risk of Bleeding

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

7 DRUG INTERACTIONS

7.1 Effect of CYP2C8 Inhibitors and Inducers on Treprostinil

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Hepatic Insufficiency
- 8.7 Patients with Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Clinical Trials in Pulmonary Arterial Hypertension (PAH)
- 14.2 Flolan-To-Remodulin Transition Study

16 HOW SUPPLIED / STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Remodulin 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), reserve 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 PAH requiring transition from Flolan (epoprostenol sodium), Remodulin 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

Remodulin can be administered without further dilution for subcutaneous administration, or diluted for intravenous infusion with Sterile Diluent for Remodulin or similar approved high-pH glycine diluent (e.g. Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium), Sterile Water for Injection, or 0.9% Sodium Chloride Injection prior to administration. See Table 1 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 Diluent for Remodulin Sterile Diluent for Flolan Sterile Diluent for Epoprostenol Sodium	14 days at room temperature	48 hours at 40°C
	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

Remodulin is 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, 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 Remodulin (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 (5.2)*]. 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, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight. Remodulin 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.

Subcutaneous Infusion

Remodulin 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 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.

Remodulin 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 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:

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

*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, 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, 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

Diluted Remodulin 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 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 $\pm 6\%$ 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 Remodulin has been shown to be stable at ambient temperature when stored for up to 14 days using high-pH glycine diluent 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 Remodulin concentration (mg/mL) can be calculated using the following formula:

Step 1

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

The volume 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

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

The calculated volume of Remodulin 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 Remodulin concentration would be calculated as follows:

Step 1

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

The volume 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

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

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