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 mimetic 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 epoprostenol, 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 WHO Group 1 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, 2.4)
- Mild to moderate hepatic insufficiency: Decrease initial dose to 0.625 ng/kg/min.
  Severe hepatic insufficiency: No studies performed. (2.5)

Transition from Epoprostenol:
Increase the Remodulin dose gradually as the epoprostenol dose is decreased, based on constant observation of response. (2.7)

Administration:
Continuous subcutaneous infusion is the preferred mode. Use intravenous (IV) infusion if subcutaneous infusion is not tolerated. (2.1, 2.6)

----------DOSAGE FORMS AND STRENGTHS----------
- Remodulin is supplied in 20-mL vials containing 20, 50, 100, 200, or 400 mg of treprostinil (1, 2.5, 5, 10, or 20 mg/mL). (3)

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS----------
- Chronic intravenous infusions delivered using an external infusion pump with an indwelling central venous catheter are 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.
Revised: 07/2021

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

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)]*.

1.2 Pulmonary Arterial Hypertension in Patients Requiring Transition from Epoprostenol

In patients with PAH requiring transition from epoprostenol, 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 with or without further dilution with Sterile Diluent for Remodulin or similar approved high-pH glycine diluent (e.g., Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol), 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.

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).

Table 1: Selection of Diluent

Diluent	Storage Limits	Administration Limits
None	See Section 16	16 weeks at 40°C
Sterile Diluents for Remodulin, Flolan, or Epoprostenol	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 Initial Dose for Patients Transitioning to an Implantable Intravenous Infusion Pump

The initial dose of Remodulin should be the same as the current dose the patient is receiving using the external infusion pump at the time of transition.

2.4 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.

2.5 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)]*.

2.6 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.

Preparation

Remodulin is administered by subcutaneous or intravenous infusion at a calculated rate based on a patient's dose (ng/kg/min), weight (kg), and the Remodulin concentration (mg/mL).

For administration of ***Undiluted*** *Remodulin* the rate is calculated using the following formula:

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

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

For administration of ***Diluted*** *Remodulin*, the concentration is calculated using the following formula:

Step 1

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

The volume of Remodulin Injection needed to make the required diluted Remodulin concentration for the given reservoir size can then be calculated using the following formula:

Step 2

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

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.

Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. The infusion pump should: (1) be adjustable to approximately 0.002 mL/hour, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of ±6% or better, (4) be positive pressure-driven, and (5) have a reservoir made of polyvinyl chloride, polypropylene or glass. Alternatively, use an infusion pump cleared for use with Remodulin. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets.

Intravenous Infusion

External Intravenous Infusion Pump:
Remodulin is administered intravenously by continuous infusion via a surgically placed indwelling central venous catheter using an external 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 increases the risk of thrombophlebitis. The infusion pump used to administer Remodulin should: (1) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (2) have delivery accuracy of ±6% or better, (3) be positive pressure driven, and (4) have a reservoir made of polyvinyl chloride, polypropylene or glass. Alternatively, use an infusion pump cleared for use with Remodulin. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets.

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

Implantable Intravenous Infusion Pump:
Use an implantable intravenous infusion pump approved for use with Remodulin, such as the Implantable System for Remodulin® (ISR). Refer to the pump manufacturer's manual for specific instructions regarding preparation, programing, implantation, and refilling.

2.7 Patients Requiring Transition from Epoprostenol

Transition from epoprostenol to Remodulin is accomplished by initiating the infusion of Remodulin and increasing it, while simultaneously reducing the dose of intravenous epoprostenol. 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).

Initiate Remodulin at a recommended dose of 10% of the current epoprostenol dose, and then escalate as the epoprostenol dose is decreased (see Table 2 for recommended dose titrations).

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

Table 2: Recommended Transition Dose Changes

Step	Epoprostenol Dose	Remodulin Dose
1	Unchanged	10% Starting Epoprostenol Dose
2	80% Starting Epoprostenol Dose	30% Starting Epoprostenol Dose
3	60% Starting Epoprostenol Dose	50% Starting Epoprostenol Dose
4	40% Starting Epoprostenol Dose	70% Starting Epoprostenol Dose
5	20% Starting Epoprostenol Dose	90% Starting Epoprostenol Dose
6	5% Starting Epoprostenol Dose	110% Starting Epoprostenol Dose
7	0	110% Starting Epoprostenol 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).
20-mL vial containing 400 mg treprostinil (20 mg per mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Catheter-Related Bloodstream Infection

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

In an open-label study of IV treprostinil (n=47) using an external infusion pump, 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.

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