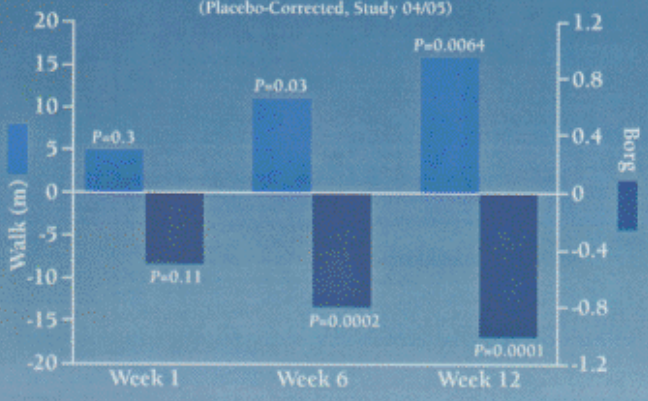
REMODULIN® (treprostinil sodium) Injection Therapy For Patients with Pulmonary Arterial Hypertension

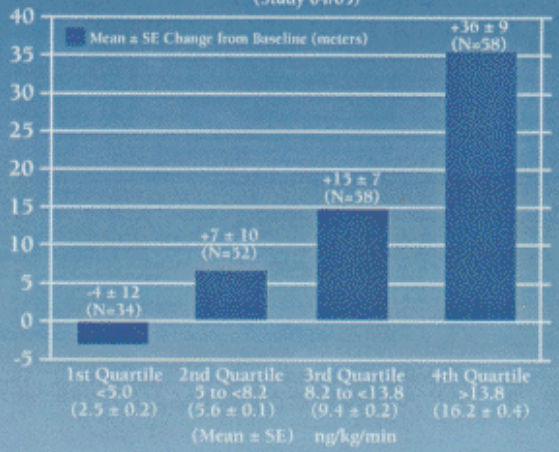
Effect of Treprostinil on Distance and Symptoms During 6-Minute Walk Test

(Placebo-Corrected, Study 04/05)



Change in Exercise vs. Treprostinil Dose at Week 12

(Study 04/05)



REMODULIN is a Stable Prostacyclin Analogue for the treatment of Pulmonary Arterial Hypertension in patients to reduce symptoms with associated with exercise intolerance in patients with NYHA Class II, III or IV Symptoms by a continuous subcutaneous infusion.

During the course of Studies 04/05, patients in the treprostinil group not only experienced a progressive increase in the distance traversed but also a progressive decrease in the shortness of breath symptoms experienced during the 6-minute walk test (as measured by the Borg Dyspnea Scores).

Significant improvement in exercise tolerance (walk distance) occurred when effective doses were reached.

Remodulin Therapy Offers:

- Decreased shortness of breath symptoms and increased exercise ability.
- Reduced invasiveness of delivery route (subcutaneous infusion versus intravenous infusion).
- Long half-life (2 to 4 hours).
- Reduced risk of infection related to administration.
- Uses an Infusion system that is lightweight and easily concealed.

Remodulin is only available from these U.S. Specialty Pharmacies:

- Accredo 1-866-344-4874 (1-866 FIGHT PH).
- Caremark RX 1-866-879-2348.
- Priority Healthcare 1866-474-8326 (1-866 4 PH TEAM).

Important Safety Information for Physicians and Patients:

- Localized infusion site pain and reaction is a common side effect, but has not been found to be dose related.
- Uncontrolled site pain or reaction management may require the use of an alternate therapy.
- Infusions must be continuous without interruption.
- Contraindicated in patients with known hypersensitivities to the drug or structurally related compounds.
- Drug interactions with antihypertensive compounds may exacerbate blood pressure reduction.
- Remodulin inhibits platelet aggregation. Use caution when combining with anticoagulants

Visit our website at www.REMODULIN.com

Please see brief summary of prescribing information on the following page.

(Photo courtesy of Medtronic MiniMed®)

United Therapeutics CORPORATION

PRODUCT INFORMATION

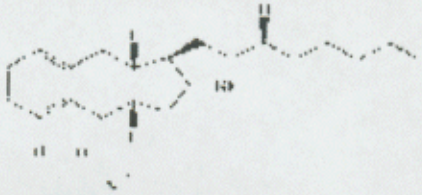
REMODULIN™ (treprostinil sodium) Injection

DESCRIPTION

Remodulin (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL or 10.0 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10.0 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. Treprostinil is chemically stable at room temperature and neutral pH.

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 sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$.

The structural formula of treprostinil sodium is:



CLINICAL PHARMACOLOGY

General: The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Pharmacokinetics

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 pg/L) 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.

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 pg/L.

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 pg/L was 91% bound to human plasma protein.

Metabolism: Remodulin is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of in vitro human hepatic cytochrome P450 studies, 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 2-4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

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 Cmax that was increased 2-fold and 4-fold, respectively, and AUC 0-∞ 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: 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, 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.

Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared Remodulin to placebo in a total of 470 patients with NYHA Class II-IV pulmonary arterial hypertension (PAH). PAH was primary in 58% of patients, associated with collagen vascular disease in 19%, and the result of congenital 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 **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 1, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

Clinical Effects

The effect of Remodulin on 6-minute walk, the primary end point of the 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. 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.

INDICATIONS AND USAGE

Remodulin™ is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms (see **CLINICAL PHARMACOLOGY:** Clinical Effects) to diminish symptoms associated with exercise.

CONTRAINDICATIONS

Remodulin is contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

WARNINGS

Remodulin is indicated for subcutaneous use only.

PRECAUTIONS

General

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. Subcutaneous 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.

Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacological 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 catheter, via an infusion pump. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept, place, and care for a subcutaneous catheter and to use an infusion pump should be carefully considered. Additionally, patients should be aware that subsequent disease management may require the initiation of an intravenous therapy.

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.

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.

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

Effect of Remodulin on Other Drugs

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

Hepatic and Renal Impairment

Caution should be used in patients with hepatic or renal impairment (see **SPECIAL POPULATIONS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. In vitro and in vivo mutagenicity studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusion 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/m2 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.

Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusion of treprostinil sodium during the period of 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/m2 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 infusion 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/m2 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.

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.

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.

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.

ADVERSE REACTIONS

Patients receiving Remodulin 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 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.

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea.

Adverse Events During Chronic Dosing: Table 3 lists adverse events that occurred at a rate of at least 3% and were more frequent in patients treated with Remodulin than with placebo in controlled trials in PAH.

Reported adverse events (at least 3%) 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.

Adverse Events Attributable to the Drug Delivery System in PAH Controlled Trials

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. Most delivery system complications were easily managed (e.g., replace syringe or battery, reprogram pump, straighten crimped infusion line). 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. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration.

OVERDOSAGE

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

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).

DOSAGE AND ADMINISTRATION

Remodulin™ is supplied in 20 mL vials in concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL. Remodulin is meant to be administered without further dilution.

Initial Dose

Remodulin is administered by continuous subcutaneous infusion. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments

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

The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks 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

Remodulin is administered by continuous subcutaneous 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 ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion rates are calculated using the following formula.

Infusion Rate (mL/hr) =
Dose (ng/kg/min) x **Weight** (kg) x [**0.00006/Remodulin dosage strength concentration** (mg/mL)]

HOW SUPPLIED

Remodulin™ is supplied in 20 mL multi-use vials at concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinil sodium equivalent to 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, or 10.0 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 Remodulin can be administered up to 72 hours at 37°C. A single vial of Remodulin should be used for no more than 14 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 treprostinil sodium equivalent to 1.0 mg treprostinil per mL, carton of 1 (NDC 66302-101-01).

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

20-mL vial containing treprostinil sodium equivalent to 5.0 mg treprostinil per mL, carton of 1 (NDC 66302-105-01).

20-mL vial containing treprostinil sodium equivalent to 10.0 mg treprostinil per mL, carton of 1 (NDC 66302-110-01).

US Patent No. 5,153,222 (Use Patent)
United Therapeutics Corp.
Research Triangle Park, NC 27709

REMODULIN manufactured by:
Baxter Pharmaceutical Solutions LLC
Bloomington, IN 47403
For United Therapeutics Corp.
Research Triangle Park, NC 27709

Rx only

March 2002

Remodulin® Medical Frequently Asked Questions

An FAQ that covers medical issues regarding the PH drug Remodulin

Acknowledgement:

Thank you to Dr. Michael McGoon for validating the answers to these questions created and presented by United Therapeutics as they currently appear in this booklet and on the PHA Interactive Web Site.

Disclaimer:

The information is provided for general information only. It is not intended as legal, medical or other professional advice, and should not be relied upon as a substitute for consultations with qualified professionals who are familiar with your individual needs.

www.phassociation.org

Q What is Remodulin?

A Remodulin (treprostinil sodium) Injection is a man-made chemical cousin (analogue) to prostacyclin (a naturally occurring chemical in the body that helps to regulate the size or diameter of the blood vessels). It is given as a continuous subcutaneous (into the skin) infusion by a small portable electronic infusion pump.

Q What is Remodulin used for?

A Remodulin was approved in May 2002 for the treatment of pulmonary arterial hypertension (PAH) in patients with New York Heart Associate Classes II, III, and IV to diminish or reduce symptoms associated with exercise. The classes refer to the severity of heart failure measured by physical activity of exercise tolerance. Class I is the most mild, and Class IV the most severe.

Q Who can prescribe Remodulin?

A Remodulin can be prescribed by any physician, but it is highly recommended the physician be well trained in treating PAH and have experience using Remodulin or with prostacyclin infusions. In addition, the physician should perform a variety of diagnostic tests to confirm the presence of PAH and to measure the severity. No medications for treating PAH should be started until a measurement of the pulmonary artery pressures are made by means of a heart catheterization.

Q How is Remodulin Therapy different from Flolan Therapy?

A Remodulin and Flolan are similar chemically, but they are not "generic" or identical. Both are prostacyclins, and both are injections requiring an electronic portable pump. Flolan is given by a continuous (24 hours a day, 7 days a week) intravenous infusion into a surgically placed catheter (tube) into the chest while Remodulin is given by a continuous infusion directly into the skin (subcutaneous).

Although both therapies use a portable infusion pump, the pump used for Flolan therapy is fairly large and not easy to conceal. Also, if the medication container (called a cassette) is to be used for more than 8 hours, ice packs need to be placed into the pump's carry pouch to keep Flolan cold. This adds to the weight of the set-up. The infusion pump for Remodulin is small, about the size of a pager/beeper, is light weight, and is easily concealed under clothing. Since Remodulin is stable at room temperature, there is no need for ice packs or other refrigerants. With special devices that go over the pump, patients can shower or bathe.

Flolan comes as a dry powder that must be mixed with a special liquid (diluent) and most patients on Flolan mix up more than one vial of drug a day. Mixed Flolan must use ice packs attached to the pump if it isn't all going to be used within 8 hours. Remodulin doesn't need mixing and is stable at room temperature and uses a smaller pump that is easily concealed. Finally, since Remodulin is given into the skin, there have been no reported infections associated with the drug delivery system. Surgically placed catheters have a risk of developing an infection over a period of time. Since Remodulin has a longer half-life (the time it takes to remove the dose from the body) of 2-4 hours than Flolan which is 2-7 minutes, the risk of rebound PAH symptoms is much less with Remodulin. Although both Remodulin and Flolan control the symptoms of PAH, there have been no clinical studies of efficacy comparing one drug to the other. Physicians need to make individual decisions on which therapy is right for their patients, but both Flolan and Remodulin require patients and their loved ones to be committed to managing the therapy.

Q How soon will I feel better once I start using Remodulin?

A Changes in exercise tolerance (your ability to have more physical activity) or improvements of PAH symptoms will vary from person to person. In Remodulin's clinical trials, walking distance increased by about 10 meters (slightly over 30 feet) and their symptoms of PAH improved (shortness of breath and fatigue) after 12 weeks of therapy.

Q **I heard there is pain associated with Remodulin. How bad is it?**

A Because Remodulin is a prostacyclin molecule and is similar to prostaglandin which is known to cause inflammation, Remodulin can cause local pain where the subcutaneous (in the skin) catheter is placed during or shortly after the infusion starts. However, the severity of pain differs from person to person. Some patients describe it similar to the pain of a tooth ache, others describe it more severely. It should be noted, there have been patients who are not able to tolerate the infusion site pain, no matter what medications or other pain relieving techniques are used. However, there are quite a few patients who have some pain at the start of their therapy but the longer they receive Remodulin, the pain diminishes especially as their PAH symptoms improve and they begin to feel better.

Q **If I have pain with Remodulin, what can I do to treat the pain?**

A There are a variety of pain relief techniques that can be tried. Your doctor and their PAH nurse can prescribe or recommend a pain management therapy that's right for your needs. Unfortunately, there is no one method that works well for everyone. Treatments that have been used that don't involve medicine are hot or cold compresses to previously used site and relaxation techniques. If medicine is needed, doctors have prescribed several medicines you take by mouth like over the counter analgesics (ibuprofen, Tylenol), stronger prescription pain relievers, and medicines that alter the sensation of pain.

There is a topical gel that is made up by a pharmacist called Pleuronic Lecithin Organogel ("PLO") which has also been called the Wisconsin Protocol. PLO Gel has several different types of medicines in very low concentrations that are applied to the skin to decrease pain and inflammation. It has worked for infusion sites that were previously used, but it is difficult to use on current or active infusion sites where pain is present because the gel doesn't allow the semi-clear dressing/tape to hold the needle in place from sticking to the skin.

For active site pain, many doctors are using the allergy drug Nasocort which is a mild steroid. Nasocort is actually a nasal spray, but when you spray it on the skin, it leaves no greasy residue and allows the dressing/tape to stick to the skin. Combining Nasocort for the active sites, and PLO Gel for the older/previously used sites is another good option to consider for patients.

There is a commercially available local anesthetic patch (called Lidoderm) which contains the drug lidocaine HCl. It is placed on the skin at the spot where the infusion needle/catheter will be placed. The infusion needle is placed through the patch, then covered with a transparent dressing to hold everything in place. Several physicians have tried this process, so you should check with your physician for more information about using Lidoderm.

Finally, other methods being considered or tried are different types of dressings/tapes that better stick to the skin so that gels or creams can be used on the active site. Keeping the needle in the skin longer than three days but no more than a week (to prevent the risk of a skin infection) has worked for patients with "hot-spots" limiting the choices of sites to place a needle.

You should always talk to your PAH Healthcare professional before attempting or trying any pain treatment. It is very important to know that infusion site pain and reaction are not in any way related to the dose or rate of infusion.

Q **If my Remodulin Infusion is interrupted, how long can I be off of it?**

A You should attempt to restart your Remodulin infusion as quickly as possible even though Remodulin has a longer half-life (longer effect of 2-4 hours) than Flolan (2-7 minutes). This is the main reason to have a back-up infusion pump and additional supplies with you at all times just in case. If you don't think your Remodulin infusion can be restarted fairly quick, you should immediately contact your doctor or seek emergency medical services for help.

Q Can I just restart Remodulin after any interruption?

A Normally yes and at the same dose or infusion rate. However, if you experience shortness of breath or other symptoms of PAH, you should contact your doctor.

Q How often will I need to adjust my Remodulin dose?

A Every patient is dosed individually to their symptoms. In other words, no one particular dose is used by all patients depending on their severity of the disease or response to the therapy. Your doctor from time to time will adjust your dose to adequately control your PAH symptoms while preventing side effects of receiving too much medication.

Also, it has been found that the side effects of experiencing pain is NOT related to any dose of Remodulin you are receiving.

Q How long will I have to use Remodulin?

A Since currently there is no cure for PAH, your treatments will be indefinite. There needs to be a strong commitment by the patient and their families for any treatment, especially an infused therapy like Remodulin. Your doctor, may at times, add or change additional medications to treat your individual PAH symptoms.

Q What are Remodulin's common side effects?

A Patients receiving Remodulin have reported a wide variety of side effects, many however, might be related to their underlying PAH disease (such as shortness of breath, fatigue, and chest pain). The most common side effects reported are infusion site pain and reaction, headache, diarrhea, nausea, rash, and jaw pain. You should discuss any side effects with your doctor or nurse.

Depending on the severity or ability to control the side effects, your doctor may choose to switch you to another therapy.

Q Can I go through airport security with my Remodulin infusion pump on?

A Yes, there are no reported mishaps with the x-ray of airport security systems erasing the pump's program or stopping the pump. If you do travel by airplane, you should keep your back-up pump, supplies, and additional Remodulin vials with you in your carry-on luggage so you have immediate access to them in case of problems during the flight. Depending on the airport, you may need a letter or note signed by your doctor explaining your pump and needles. Your nurse or doctor can provide you with a letter to give to the airline ahead of time to allow you to carry these supplies. You can check with the airport or the Federal Aviation Administration (FAA) for more information.

Q What if I get my Remodulin infusion pump wet?

A There are no medication infusion pumps that are waterproof so you must avoid submersing the pump in any liquid. If the pump's exterior gets wet, immediately dry the pump with a cloth (don't use a hairdryer, oven, microwave, or place the pump near high heat such as a fire). The maker of the MiniMed 407c infusion pump used in Remodulin therapy does make a special disposable shower pack that the pump is placed into to minimize the risk of a pump getting wet when taking a shower or bath. MiniMed makes a "swim pack" that can protect the pump for swimming purposes, however, this costs extra and is not covered by insurance. You should check with your Remodulin pharmacy provider for additional information and always check with your doctor before starting any strenuous exercise, like swimming.

Q How do you start Remodulin?

A Every center is different, however, once you and your doctor decide this is the treatment to use, the nurse coordinator orders the drug. It can take as little as 24 hours or as long as six weeks or more to approve it through the insurance company. Once it is approved, a nurse can come to your home to start "pre-teaching". The drug needs to be started in the doctor's office the first time. This visit can last anywhere from 2 to 8 hours, depending on what your needs are.

A home care nurse can continue to see you for the "re-injections" every three days for several visits, again depending on your insurance company.

Q **Can I switch from Flolan to Remodulin?**

A Yes, in fact there were published results of a study where patients were successfully switched from Flolan to Remodulin. Switching from one drug to another requires your doctor to be very knowledgeable about both drugs and switching drugs will require hospitalization to wean you off Flolan as you start Remodulin. This way your doctor can determine which Remodulin dose is right for your particular condition. Patients on Remodulin compared to Flolan have more freedom of movement and activities due to a smaller pump and no surgically placed catheter to administer the drug. However, there are side effects of site pain and infusion site reaction when using that can occur when using Remodulin which doesn't occur with Flolan.

For more information about pulmonary hypertension, you can contact the Pulmonary Hypertension Association (PHA) at www.phassociation.org or 301-565-3004. PHA is an international association of patients, family members and medical professionals headquartered in Silver Spring, Maryland.

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www.remodulin.com