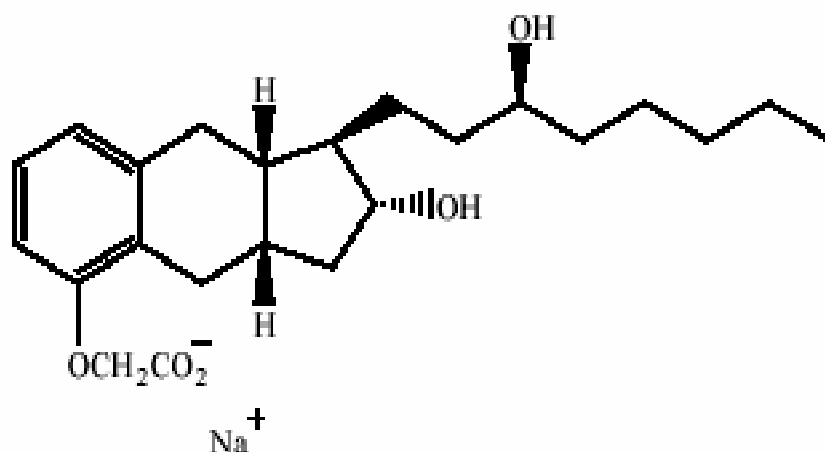


**PRODUCT INFORMATION****REMODULIN™ Injection****NAME OF DRUG**

Treprostinil sodium



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<sub>23</sub>H<sub>33</sub>NaO<sub>5</sub>.

**DESCRIPTION**

Remodulin (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous administration. The appearance of the product is clear, colourless to slightly yellow solution, essentially free from visible particulate matter. 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.

**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. Impurities in the formulation were within acceptable limits but not all were tested across the entire dose range.

## Pharmacokinetics

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 2.5 to 15 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 µg/L) and can be described by a two-compartment pharmacokinetic model. Dose proportionality at infusion rates greater than 15 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 9.2 ng/kg/min were approximately 2 µg/L.

### Distribution

The volume of distribution of the drug in the plasma is approximately 0.2L/kg ideal body weight. Remodulin at in vitro concentrations ranging from 330-10,000 µg/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 faeces. 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 C<sub>max</sub> that was increased 2-fold and 4-fold, respectively, and AUC<sub>0-∞</sub> 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.

### *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.

## CLINICAL TRIALS

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 dyspnoea 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.

There is no controlled efficacy data beyond 12 weeks. Survival has not been evaluated in the clinical trials.

### Haemodynamic Effects

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

**Table 1: Haemodynamics During Chronic Administration of Remodulin in Patients with PAH**

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 <sup>2</sup> )	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 <sup>2</sup> )	26 ± 13	25 ± 13	-3.5 ± 8.2*	+1.2 ± 7.9
SVRI (mmHg/L/min/m <sup>2</sup> )	38 ± 15	39 ± 15	-3.5 ± 12*	-0.80 ± 12
SvO <sub>2</sub> (%)	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; SvO<sub>2</sub> = mixed venous oxygen saturation; HR = heart rate.

### Clinical Effects

The effect of Remodulin on 6-minute walk, the primary endpoint of the studies, was small and did not reach conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 metres and the median change from baseline on placebo was 0 metres, the median between-treatment difference over placebo was 16 metres.

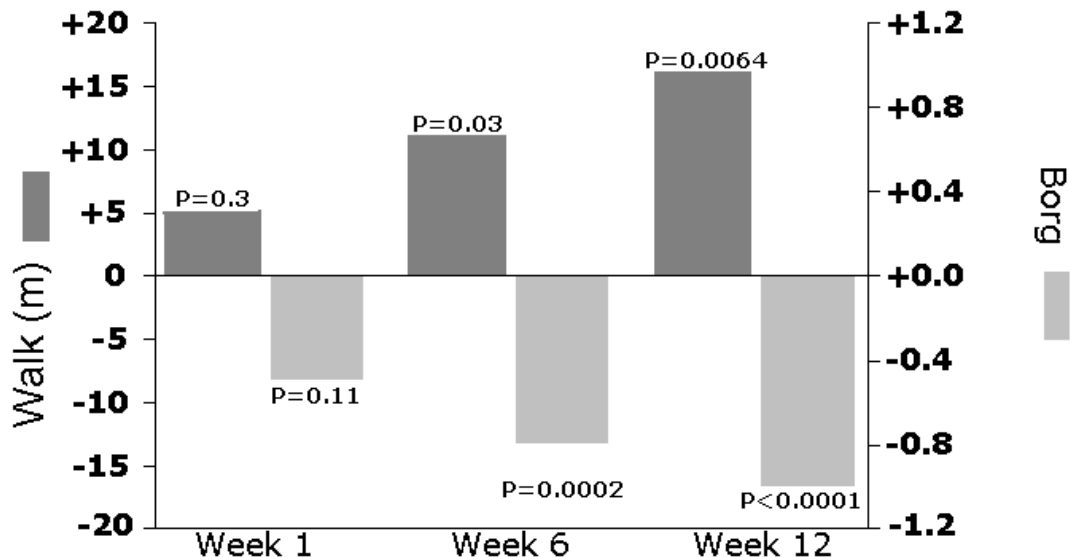
**Table 2: Effects of Remodulin on 6-minute walk distance at Week 12 (Protocol P01:04 and P01:05 (combined))**

	Protocols P01:04 and P01:05 (medians)	
	Remodulin (N=237)	Placebo (N=236)
Baseline	345 m	342 m
Change from Baseline	10 m	0 m
Treatment Difference*	16 m	

\* Hodges-Lehmann Difference with 95% confidence interval (4.4, 27.6);  $p=0.0064$  by nonparametric analysis of covariance

Although it was not the primary endpoint of the study, the Borg dyspnoea 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 dyspnoea score.

**Figure 1: Median treatment difference over placebo in six-minute walk and Borg-Dyspnoea Scores for Weeks 1, 6 and 12**



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.

The total number of deaths, transplantations or discontinuations due to clinical deterioration was also assessed. The total number was greater in the placebo group (16 patients versus 13 patients), but the between-group differences were not significantly different (Table 3).

**Table 3: Deaths/Transplants/Deteriorations Requiring Rescue (Protocols P01:04/P01:05 Combined)**

Endpoint	Remodulin (n=233)	Placebo (n=237)
Deaths/Transplants/Rescue	13	16
Deaths During Study Period	9	10
Deaths on Drug	7	7
Transplants	0	1
Need for Rescue	6	6

## INDICATIONS

Remodulin is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA class III-IV to diminish symptoms associated with exercise.

## CONTRAINDICATIONS

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

## PRECAUTIONS

### *General*

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

Remodulin is indicated for subcutaneous use only. Use of a peripheral IV infusion may be associated with an increased risk of thrombophlebitis.

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 sanitary conditions and the ability to use sterile technique to administer Remodulin and care for an infusion system should be carefully considered. Patients will require comprehensive training and education on using the Infusion system before being able to self-administer the drug. The patient should be advised that the subcutaneous infusion site catheter should be changed every 3 days.

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**).

Injection site pain and reactions are the most common cause of discontinuations and lead to increased narcotic usage amongst treprostinil patients.

Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided. Deaths have been reported. Discontinuation from therapy should involve gradual weaning over at least a 24 hour period. Similarly, transition to and from drugs with a similar action should take place using a process of simultaneous titration over at least 24 hours.

Haemorrhage from non-injections sites was observed in 38 patients on treprostinil vs 17 on placebo, specifically gastrointestinal bleeding (11 vs 2) and epistaxis (12 vs 4). Two patients also died from haemorrhage.

The safety and efficacy of substituting intravenous epoprostenol (Flolan) therapy with subcutaneous treprostinil (Remodulin) has not been established.

Rapid dose escalation of Remodulin should be administered with caution in patients with intra-cardiac shunts due to the risk of pulmonary hypertensive crises.

### ***Carcinogenicity and Mutagenicity***

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. Genotoxicity studies did not demonstrate any mutagenic or clastogenic effects in bacteria or mouse lymphoma cells *in vitro* and in rat bone marrow erythrocytes *in vivo*.

### ***Impairment of Fertility***

Treprostinil sodium did not affect fertility or mating performance of male or female rats at continuous SC infusion rates of up to 450 ng treprostinil/kg/min, resulting in exposure 13 times the clinical exposure (based on plasma  $C_{ss}$ ) at an infusion rate of 15 ng/kg/min.

### ***Use in Pregnancy***

Pregnancy Category B3: Treprostinil was not teratogenic in rats or rabbits dosed with up to 900 and 300 ng/kg/min, respectively, by continuous SC infusion during organogenesis. Placental transfer was not determined in animal studies. In pregnant rabbits, embryofetal effects of treprostinil were limited to an increased incidence of fetal skeletal variations (bilateral full rib or rudimentary right rib on the first lumbar vertebra), associated with maternal toxicity, at  $\geq 150$  ng/kg/min (about 5 times the clinical exposure based on plasma  $C_{ss}$  at an infusion rate of 15 ng/kg/min). The incidence of enlarged nasal sinus of fetuses, (associated with maternal toxicity), was slightly increased in pregnant rats at  $\geq 450$  ng/kg/min ( $\geq 10$  times the clinical exposure based on plasma  $C_{ss}$  at a clinical dose of 15 ng/kg/min). Effects on mating rate of  $F_1$  rats were observed at the same dose (see **Use in Lactation**). Duration of gestation and parturition was unaffected in pregnant rats at up to 450 ng/kg/min. The effect of treprostinil on labour and delivery in humans is unknown.

Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

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.

**Use in lactation**

It is not known whether treprostinil is excreted in animal or human milk. Mating rate was decreased in F<sub>1</sub> rats, which were raised from dams treated with treprostinil at 450 ng/kg/min (10 times the clinical exposure based on C<sub>ss</sub> at 15 ng/kg/min) by continuous SC infusion during gestation and lactation. Because many drugs are excreted in human milk, nursing women taking Remodulin should stop breast feeding.

**Hepatic and Renal Impairment**

Caution should be used in patients with hepatic or renal impairment (see **DOSAGE AND ADMINISTRATION** and **Special Populations**).

**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.

**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. Clearance was reduced in the elderly. 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.

**Obesity**

See Dosage and Administration section.

**Driving and Operating Machinery**

Remodulin and its therapeutic management may affect the ability to drive and operate machinery.

**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: Paracetamol - Analgesic doses of paracetamol, 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).

The concomitant use of other vasodilators may augment the vasodilator effects of treprostinil.

The concomitant use of NSAIDs or other drugs affecting platelet aggregation may increase the risk of bleeding.

Multivariate analysis involving 186 patients with PAH in the pivotal studies, showed that frusemide reduced the treprostinil clearance by approximately 22%.

### **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.

## **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 subcutaneous infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Injection site bleeding and bruising were also very common. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

**Table 4: Percentages of subjects reporting subcutaneous infusion site adverse events**

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

\* based on prescriptions for narcotics, not actual use

\*\* medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Other adverse events included diarrhea, jaw pain, oedema, gastrointestinal bleeding, epistaxis, vasodilatation, nausea, right ventricular failure, supraventricular tachycardia and infusion site infection.

Small but significant reductions in RBC, Hb, HCT, WBC, BUN, LDH and bilirubin and small but significant increases in eosinophils and platelet counts have been reported.

**Table 5: Frequency of Adverse Events Regardless of Attribution Occurring in >1% of Patients with PAH Treated with Remodulin in Placebo Controlled Studies**

Adverse Event	Remodulin (N=236) N (%)	Placebo (N=233) N(%)
<b><i>OCCURRENCE MORE COMMON WITH REMODULIN</i></b>		
<b>Skin and Appendages</b>		
Infusion site pain	200 (84.7)	62 (26.6)
Infusion site reaction	196 (83.1)	62 (26.6)
Rash	32 (13.6)	26 (11.2)
Pruritis	19 (8.1)	15 (6.4)
Contact Dermatitis	3 (1.3)	1 (0.4)
Injection site reaction	3 (1.3)	0 (0.0)
<b>General (Body as Whole)</b>		
Headache	64 (27.1)	54 (23.2)
Jaw pain	31 (13.1)	11 (4.7)
Pain	28 (11.9)	25 (10.7)
Infection	21 (8.9)	20 (8.6)
Flu Syndrome	11 (4.7)	9 (3.9)
Asthenia	11 (4.7)	7 (3.0)
Sweating	3 (1.3)	1 (0.4)
Overdose	3 (1.3)	0 (0.0)
<b>Gastrointestinal (Digestive)</b>		
Diarrhea	58 (24.6)	36 (15.5)
Nausea	52 (22.0)	41 (17.6)
Anorexia	11 (4.7)	4 (1.7)
Nausea and Vomiting	7 (3.0)	2 (0.9)
Melena	5 (2.1)	0 (0.0)
Rectal Hemorrhage	3 (1.3)	0 (0.0)
<b>Cardiovascular</b>		
Hypotension	9 (3.8)	6 (2.6)
Tachycardia	4 (1.7)	3 (1.3)
Palpitation	3 (1.3)	2 (0.9)
Hypertension	3 (1.3)	0 (0.0)
<b>Metabolic and Nutritional</b>		
Edema	21 (8.9)	6 (2.6)
Hypokalemia	5 (2.1)	0 (0.0)
Gout	3 (1.3)	1 (0.4)
Dehydration	3 (1.3)	0 (0.0)
<b>Musculoskeletal</b>		
Myalgia	3 (1.3)	1 (0.4)
<b>Neurological/Nervous</b>		
Vasodilatation	25 (10.6)	11 (4.7)
Dizziness	21 (8.9)	19 (8.2)
Insomnia	14 (5.9)	8 (3.4)
Anxiety	7 (3.0)	6 (2.6)
Paresthesia	3 (1.3)	2 (0.9)
<b>Respiratory</b>		
Epistaxis	10 (4.2)	4 (1.7)
Hypoxia	4 (1.7)	1 (0.4)
<b>Urogenital</b>		
Urinary Tract Infection	4 (1.7)	3 (1.3)

**Table 5: Frequency of Adverse Events Regardless of Attribution Occurring in >1% of Patients with PAH Treated with Remodulin in Placebo Controlled Studies (continued)**

Adverse Event	Remodulin (N=236) N (%)	Placebo (N=233) N(%)
<b>OCCURRENCE AS COMMON OR MORE COMMON WITH PLACEBO</b>		
<b>Skin and Appendages</b>		
Infusion site bleed/bruise	79 (33.5)	102 (43.8)
Skin Ulcer	1 (0.4)	4 (1.7)
<b>Hematologic and Lymphatic</b>		
Ecchymosis	9 (3.8)	27 (11.6)
Anemia	3 (1.3)	3 (1.3)
<b>Body</b>		
Chest Pain	10 (4.2)	20 (8.6)
Abdominal Pain	8 (3.4)	10 (4.3)
Back Pain	6 (2.5)	11 (4.7)
Fever	6 (2.5)	10 (4.3)
Neck pain	2 (0.8)	5 (2.1)
Cellulitis	3 (1.3)	3 (1.3)
Malaise	2 (0.8)	3 (1.3)
Viral Infection	1 (0.4)	3 (1.3)
<b>Cardiovascular</b>		
Heart Failure	7 (3.0)	17 (7.3)
Hemorrhage	7 (3.0)	13 (5.6)
Syncope	7 (3.0)	12 (5.2)
Bradycardia	3 (1.3)	3 (1.3)
<b>Gastrointestinal (Digestive)</b>		
Vomiting	12 (5.1)	14 (6.0)
Dyspepsia	3 (1.3)	6 (2.6)
<b>Metabolic and Nutritional</b>		
Peripheral Edema	11 (4.7)	16 (6.9)
<b>Neurological/Nervous</b>		
Depression	3 (1.3)	6 (2.6)
Nervousness	1 (0.4)	3 (1.3)
<b>Respiratory</b>		
Pharyngitis	13 (5.5)	21 (9.0)
Dyspnoea	8 (3.4)	19 (8.2)
Cough	7 (3.0)	19 (8.2)
Sinusitis	4 (1.7)	9 (3.9)
Pulmonary Hypertension	4 (1.7)	6 (2.6)
Bronchitis	2 (0.8)	6 (2.6)
Rhinitis	5 (2.1)	5 (2.1)
Hemoptysis	4 (1.7)	5 (2.1)
<b>Musculoskeletal</b>		
Leg Cramps	2 (0.8)	5 (2.1)
Arthralgia	2 (0.8)	3 (1.3)

Serious Adverse Events (SAE's) were common (17% in treprostinil patients), but drug-related SAE's were only those related to prostaglandin-like drugs. Incidence of life-threatening hypotension and syncope was low. However, treprostinil-related vomiting and diarrhoea could be protracted and serious. The incidence of discontinuations due to adverse events was much higher in the treprostinil group compared to placebo (18 vs 1). Severe infusion site pain and reactions were the most common causes of discontinuations due to adverse events. Chronic subcutaneous treatment with treprostinil did not have any clinically significant effect on vital signs, haematology or clinical chemistry values.

### **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., dyspnoea). 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.

### **Post-marketing experience**

Generalised rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported in post-marketing experience.

The following events have also been identified during post-approval use of Remodulin:

- Thrombophlebitis associated with peripheral intravenous infusion
- Infusion site infection
- Subcutaneous infusion site abscess formation
- Thrombocytopenia
- Bleeding associated with the infusion site and
- Bone pain

## **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. The product is intended for use as a multidose vial in individual patients only.

### **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 withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided. Deaths have been reported. Discontinuation from therapy should involve gradual weaning over at least a 24 hour period. Similarly, transition to and from drugs with a similar action should take place using a process of simultaneous titration over at least 24 hours.

### ***Hepatic Impairment***

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

### ***Renal Impairment***

Based on individual patient dose titration recommended for Remodulin, doses of Remodulin should be increased more conservatively in patients with renal insufficiency (see **Special Populations**).

### ***Obesity***

Multivariate analysis showed that treprostinil clearance was reduced by approximately 36% in obese patients. Hence, dosing based on ideal body weight may have to be considered for obese PAH patients.

### ***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  $\pm 6\%$  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)]**

Tables 6 through 9 provide Remodulin infusion delivery rates for doses up to 100 ng/kg/min, based on patient weight, drug delivery rate and concentration. These tables may be used to select the most appropriate concentration and infusion rate for Remodulin. No dilution is necessary.

Table 6

**1.0 mg/ml Concentration of Remodulin™**  
**Pump Infusion Rate Setting (mL/hr) for 1.0 mg/mL Remodulin**  
**Patient Weight (kg)**

Dose (ng/kg/min)	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
1.25	0.002	0.002	0.003	0.003	0.003	0.004	0.004	0.005	0.005	0.005	0.006	0.006	0.006	0.007	0.007	0.008
2.5	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
3.75	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021	0.023
5	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
6.25	0.009	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.024	0.026	0.028	0.030	0.032	0.034	0.036	0.038
7.5	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
8.75	0.013	0.016	0.018	0.021	0.024	0.026	0.029	0.032	0.034	0.037	0.039	0.042	0.045	0.047	0.050	0.053
10	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
11.25	0.017	0.020	0.024	0.027	0.030	0.034	0.037	0.041	0.044	0.047	0.051	0.054	0.057	0.061	0.064	0.068
12.5	0.019	0.023	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
13.75	0.021	0.025	0.029	0.033	0.037	0.041	0.045	0.050	0.054	0.058	0.062	0.066	0.070	0.074	0.078	0.083
15	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
16.25	0.024	0.029	0.034	0.039	0.044	0.049	0.054	0.059	0.063	0.068	0.073	0.078	0.083	0.088	0.093	0.098
17.5	0.026	0.032	0.037	0.042	0.047	0.053	0.058	0.063	0.068	0.074	0.079	0.084	0.089	0.095	0.100	0.105
18.75	0.028	0.034	0.039	0.045	0.051	0.056	0.062	0.068	0.073	0.079	0.084	0.090	0.096	0.101	0.107	0.113
20	0.030	0.036	0.042	0.048	0.054	0.060	0.066	0.072	0.078	0.084	0.090	0.096	0.102	0.108	0.114	0.120
21.25	0.032	0.038	0.045	0.051	0.057	0.064	0.070	0.077	0.083	0.089	0.096	0.102	0.108	0.115	0.121	0.128
22.5	0.034	0.041	0.047	0.054	0.061	0.068	0.074	0.081	0.088	0.095	0.101	0.108	0.115	0.122	0.128	0.135
23.75	0.036	0.043	0.050	0.057	0.064	0.071	0.078	0.086	0.093	0.100	0.107	0.114	0.121	0.128	0.135	0.143
25	0.038	0.045	0.053	0.060	0.068	0.075	0.083	0.090	0.098	0.105	0.113	0.120	0.128	0.135	0.143	0.150
27.5	0.041	0.050	0.058	0.066	0.074	0.083	0.091	0.099	0.107	0.116	0.124	0.132	0.140	0.149	0.157	0.165
30	0.045	0.054	0.063	0.072	0.081	0.090	0.099	0.108	0.117	0.126	0.135	0.144	0.153	0.162	0.171	0.180
32.5	0.049	0.059	0.068	0.078	0.088	0.098	0.107	0.117	0.127	0.137	0.146	0.156	0.166	0.176	0.185	0.195
35	0.053	0.063	0.074	0.084	0.095	0.105	0.116	0.126	0.137	0.147	0.158	0.168	0.179	0.189	0.200	0.210
37.5	0.056	0.068	0.079	0.090	0.101	0.113	0.124	0.135	0.146	0.158	0.169	0.180	0.191	0.203	0.214	0.225
40	0.060	0.072	0.084	0.096	0.108	0.120	0.132	0.144	0.156	0.168	0.180	0.192	0.204	0.216	0.228	0.240
42.5	0.064	0.077	0.089	0.102	0.115	0.128	0.140	0.153	0.166	0.179	0.191	0.204	0.217	0.230	0.242	0.255

The infusion rate for 1.0 mg/ml can be calculated using the following formula: Patient weight (kg) x dose (ng/kg/min) x 0.00006.

Table 7

**2.5 mg/ml Concentration of Remodulin™**  
**Pump Infusion Rate Setting (mL/hr) for 2.5 mg/mL Remodulin**  
**Patient Weight (kg)**

<b>Dose (ng/kg/min)</b>	<b>25</b>	<b>30</b>	<b>35</b>	<b>40</b>	<b>45</b>	<b>50</b>	<b>55</b>	<b>60</b>	<b>65</b>	<b>70</b>	<b>75</b>	<b>80</b>	<b>85</b>	<b>90</b>	<b>95</b>	<b>100</b>
<b>5</b>	0.003	0.004	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
<b>6.25</b>	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
<b>7.5</b>	0.005	0.005	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
<b>8.75</b>	0.005	0.006	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
<b>10</b>	0.006	0.007	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
<b>11.25</b>	0.007	0.008	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
<b>12.5</b>	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
<b>13.75</b>	0.008	0.010	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
<b>15</b>	0.009	0.011	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
<b>16.25</b>	0.010	0.012	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
<b>17.5</b>	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
<b>18.75</b>	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
<b>20</b>	0.012	0.014	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
<b>21.25</b>	0.013	0.015	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
<b>22.5</b>	0.014	0.016	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
<b>23.75</b>	0.014	0.017	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
<b>25</b>	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
<b>27.5</b>	0.017	0.020	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
<b>30</b>	0.018	0.022	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
<b>32.5</b>	0.020	0.023	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
<b>35</b>	0.021	0.025	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
<b>37.5</b>	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
<b>40</b>	0.024	0.029	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096
<b>42.5</b>	0.026	0.031	0.036	0.041	0.046	0.051	0.056	0.061	0.066	0.071	0.077	0.082	0.087	0.092	0.097	0.102

The infusion rate for 2.5 mg/ml can be calculated using the following formula: Patient weight (kg) x dose (ng/kg/min) x 0.000024.

Table 8

**5.0 mg/mL Concentration of Remodulin™**  
**Pump Infusion Rate Setting (mL/hr) for 5.0 mg/mL Remodulin**  
**Patient Weight (kg)**

<b>Dose (ng/kg/min)</b>	<b>25</b>	<b>35</b>	<b>40</b>	<b>45</b>	<b>50</b>	<b>55</b>	<b>60</b>	<b>65</b>	<b>70</b>	<b>75</b>	<b>80</b>	<b>85</b>	<b>90</b>	<b>95</b>	<b>100</b>
<b>10</b>	0.003	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
<b>12.5</b>	0.004	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
<b>15</b>	0.005	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
<b>17.5</b>	0.005	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
<b>20</b>	0.006	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
<b>22.5</b>	0.007	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
<b>25</b>	0.008	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
<b>27.5</b>	0.008	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
<b>30</b>	0.009	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
<b>32.5</b>	0.010	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
<b>35</b>	0.011	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
<b>37.5</b>	0.011	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
<b>40</b>	0.012	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
<b>42.5</b>	0.013	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
<b>45</b>	0.014	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
<b>47.5</b>	0.014	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
<b>50</b>	0.015	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
<b>55</b>	0.017	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
<b>60</b>	0.018	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
<b>65</b>	0.020	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
<b>70</b>	0.021	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
<b>75</b>	0.023	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
<b>80</b>	0.024	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096

The infusion rate for the 5 mg/mL concentration can be calculated by using the following formula: Patient weight (kg) x dose (ng/kg/min) x 0.000012.

Table 9

**10.0 mg/mL Concentration of Remodulin™  
Pump Infusion Rate Setting (mL/hr) for 10.0 mg/mL Remodulin  
Patient Weight (kg)**

<b>Dose (ng/kg/min)</b>	<b>35</b>	<b>40</b>	<b>45</b>	<b>50</b>	<b>55</b>	<b>60</b>	<b>65</b>	<b>70</b>	<b>75</b>	<b>80</b>	<b>85</b>	<b>90</b>	<b>95</b>	<b>100</b>
<b>50</b>	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
<b>55</b>	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
<b>60</b>	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
<b>65</b>	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
<b>70</b>	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
<b>75</b>	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
<b>80</b>	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
<b>85</b>	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
<b>90</b>	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
<b>95</b>	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
<b>100</b>	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060

The infusion rate for the 10 mg/mL concentration can be calculated by using the following formula: Patient weight (kg) x dose (ng/kg/min) x 0.000006

## 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, diarrhea or syncope. 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).

For advice on the management of overdosage, please contact the Poisons Information Centre (telephone 13 11 26).

## PRESENTATION

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.

## STORAGE CONDITIONS

Store below 25°C

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 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. Remodulin injection is a clear colourless to slightly yellow solution, essentially free from visible particulate matter.

## NAME AND ADDRESS OF THE SPONSOR

Orphan Australia Pty. Ltd.  
48 Kangan Drive  
Berwick  
Victoria 3806  
Australia

Website: [www.orphan.com.au](http://www.orphan.com.au)

## POISON SCHEDULE OF THE MEDICINE

S4

**DATE OF APPROVAL**

This Product Information was approved by the TGA on: 18 August 2005

The date of the most recent safety related notification: 20 July 2007

Remodulin is a trademark of United Therapeutics Corp.