National PBM Drug Monograph
Treprostinil Sodium Injection (Remodulin™)
Synonyms: 15AU81, Uniprost, UT-15, LRX-15, BW-15AU, U-62840

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel
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Introduction[1-2]

Pulmonary Arterial Hypertension (PAH) is a relatively rare condition affecting approximately 50,000 patients in North America and Europe. PAH is a progressive disease due to occlusion of blood vessels, and an inexorable increase in pulmonary vascular resistance, which leads to secondary right ventricular failure and death. If left untreated, the mean survival time after diagnosis is 2.8 years. Treatment options may be complex, controversial and potentially dangerous. In PAH there is a dysregulation of the prostacyclin metabolic pathways. Prostacyclin is an endogenous substance produced by endothelial cells. Prostacyclin induces vasodilation, inhibits platelet aggregation, and suppresses smooth muscle cell migration and proliferation.

The World Health Organization's diagnostic classification system categorizes Pulmonary Arterial Hypertension as Primary Pulmonary Hypertension, which may be either sporadic or familial (associated with a gene mutation). PAH is related to: collagen vascular disease (i.e. scleroderma, lupus, rheumatoid arthritis), congenital systemic to pulmonary shunts, portal hypertension and/or liver disease, HIV infection, drugs/toxins (i.e. anorexigens, amphetamines, cocaine, methamphetamine or other recreational/designer drugs, & chemotherapeutic agents), persistent pulmonary hypertension in the newborn and other non-specified causes. Hallmarks of primary pulmonary hypertension include vasoconstriction, vascular remodeling and thrombosis. Anticoagulants and vasodilators are common first line treatment options.

Since 1994, IV Epoprostenol Sodium (PGI2; PGX; Prostacyclin) a prostacyclin analogue has provided the current medical standard of care for patients suffering from New York Heart Association (NYHA) Class III & IV pulmonary hypertension. PGI2 must be administered via a permanently implanted central venous catheter. Central venous therapy with PGI2 carries the risk of sepsis, catheter related embolism, thrombosis, and delivery system malfunctions such as accidental occlusions, perforations and dislodgments of the catheter, as well as, pump malfunction. *Any* interruption in therapy may be associated with syncope and death from an acute pulmonary hypertensive crisis due to the short half-life (1-2 minutes) of PGI2.

Treprostinil Sodium (TRE) is a new prostacyclin analogue that may help reduce life-threatening complication rates associated with the central venous administration requirement of PGI2. Pharmacokinetic advantages of TRE include its longer half-life (3-4 hours) and subcutaneous route of administration. Reconstitution and/or refrigeration are not required during TRE administration as they are with PGI2. Infusion site erythema, swelling and pain have occurred with TRE treatment and have occasionally been severe enough to require discontinuation of therapy.

Treprostinil is used for the treatment of Pulmonary Arterial Hypertension (PAH). It is the first approved therapy for patients with NYHA Class II PAH, as well as for the treatment of all other symptomatic stages of the disease (II-IV). Studies show that TRE can improve exercise capacity, dyspnea scores during exercise, hemodynamics, and quality of life. TRE has been used for up to 4 years in patients participating in clinical trials. TRE's exact place in therapy will be delineated with further studies.

Pharmacology[2-4]

Chemical Entity: Treprostinil is a tricyclic benzindene analogue of Epoprostenol.

Mechanism of action: Treprostinil exerts its primary pharmacodynamic action via direct and potent vasodilation of pulmonary and systemic arterial beds and inhibition of platelet aggregation. Animal studies have shown a reduction in right and left ventricular afterload due to vasodilatory effects, as well as, an increase in cardiac output and stroke volume. Additionally, dose-related negative inotropic and lusitropic effects have been seen in other studies. Major cardiac conduction effects have not been observed.
TRE exhibits potent antiproliferative activity in human pulmonary artery smooth muscle cells via a proposed c-AMP dependent mechanism.

Pharmacokinetics[2-4]

Kinetics: Continuous subcutaneous Treprostinil infusions exhibit linear kinetics over a dose range of 1.25 to 22.5 ng/kg/min. This corresponds to a plasma concentration of approximately 0.03 to 8μg/L. Treprostinil is described by a two-compartment open model. Dose proportionality studies of infusion rates greater than 22.5ng/kg/min have not been studied.

Absorption: Subcutaneous infusions of treprostinil show rapid, complete and ~100% bioavailability. Approximately 10 hours are required for steady state concentrations to occur. Patients treated with an average dose of 9.3ng/kg/min had approximately a 2μg/L concentration.

Distribution: There is approximately a 14L/70kg ideal body weight volume of distribution of the drug in the central compartment. In vitro concentrations ranging from 330-10,000 μg/L were 91% protein bound to human plasma proteins.

Metabolism: Treprostinil undergoes substantial liver metabolism; however, the precise enzyme responsible for metabolism is unknown. There are 5 metabolites (HU1-HU5). The activity and fate of these metabolites is unknown. HU5 is a glucuronide conjugate of treprostinil. HU2 through HU4 are formed by the oxidation of the 3-hydroxyoctyl-side chain. HU3 undergoes an additional oxidation, and HU4 forms via dehydration. In vitro human hepatic P450 studies show no inhibition of CYP-1A2, 2C9, 2C19, 2D6, 2E1 or 3A by treprostinil. Enzyme induction studies have not yet been published.

Excretion: Treprostinil exhibits biphasic elimination with a terminal half-life of ~2-4 hours. Administration of treprostinil leads to about 79% of the administered dose being eliminated in the identifiable metabolites. About 13% of the dose is eliminated fecally. A 70kg ideal body weight person would have a systemic clearance of approximately 30L/hr.

Table 1: Comparison of Treprostinil and Epoprostenol[2,4,5]

	Drug: Treprostinil	**Drug: Epoprostenol**
Absorption	Subcutaneous Infusion (Rapid and complete)	IV (implanted central venous catheter)
Distribution	14L/70kg lean body weight	357 mL/kg
Metabolism	Liver (forms metabolites H1-H5))	Two primary (6-keto-prostaglandin F1-alpha & 6,15-diketo-13,14-dihydro-PGF1-alpha) metabolites with pharmacologic activity and 14 minor metabolites
Elimination	79% urine & 13% fecal	Urinary metabolites
Half-life	2-4 hour terminal half life	3-5 minutes

Protein Binding	91%	None reported
Bioavailability	~100%	100%
Stability	Stable at room temperature & neutral pH. A vial of TRE may be used for up to 14 days after the initial entry into the vial.	Unstable at room temperature. Requires refrigeration during administration and protection from light.
Reconstitution	Ready to use-no reconstitution or further dilution required prior to use	Mixing required prior to using. Note: When a cold pouch is used during administration reconstituted solutions may be used for 8 hours at room temperature or for up to 24 hours when used in combination with frozen gel packs. (Gel packs are changed every 12 hours.) Reconstituted solutions awaiting use may be stored under refrigeration for up to 48 hours.
Infusion Device	Microinfusion Device Minimed®	Portable Pump

FDA Approved Indication(s) and Off-label Uses[3,4,6,7]

The FDA issued a Final Approval Letter on May 22nd, 2002 for Treprostinil for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise. Treprostinil is administered via a continuous subcutaneous infusion. The FDA approval rating is 1P. Therapeutically TRE is classified as a Peripheral Vasodilator.

Trials examining the use of treprostinil for peripheral vascular disease (PVD), and other cardiac conditions including Congestive Heart Failure by decreasing systemic vascular resistance and increasing the cardiac index, critical limb ischemia (CLI), and metastatic cancer are on going. Animal studies suggest that pegylated formulations of TRE are effective pulmonary vasodilators when administered via the airways.

TRE may potentially have a role as an antiulcer agent or antiasthmatic agent due to its ability to reduce gastric secretions and bronchodilate.

Current VA National Formulary Status

Treprostinil has a non-formulary status.

Dosage and Administration[2-4,8]

Initial Dosage: Treprostinil is to be administered by continuous subcutaneous infusion at an initial rate of 1.25 ng/kg/min; however, if this dose is not tolerated the rate should be reduced to 0.625 ng/kg/min. Dose reductions may be due to either excess pharmacologic effects or unacceptable infusion site symptoms.

Dosage Adjustments: Treprostinil dosage should be adjusted to establish a dose whereby PAH symptoms are improved, while the pharmacologic side effects (headache, nausea, vomiting, restlessness, anxiety, and infusion site pain or reaction) are minimized.

Upward dose titrations may be initiated due to a lack of response or worsening of PAH symptoms. Weekly increases of no more than 1.25 ng/kg/min are allowed over the first four

weeks. Afterwards, increases of 2.5 ng/kg/min per week are allowed for the duration of the infusion depending on clinical response. Doses over 40 ng/kg/min have not been well studied. Abrupt discontinuation of the infusion or large dosage reductions should be avoided, as they may result in worsening of PAH symptoms.

Administration: Patients may self-administer treprostinil via continuous subcutaneous infusion. Patients will need to be trained in how to self-insert the subcutaneous catheter, and use the subcutaneous infusion pump. A back up infusion pump and subcutaneous infusion sets should be immediately available to avoid potential interruptions in drug delivery. The ambulatory infusion pump should be small and lightweight. It needs to be capable of delivering 0.002 ml/hr, and it should have occlusion/no delivery, low battery, programming error and motor malfunction alarms, have delivery accuracy of ±6% or better, and be positive pressure driven. Acceptable reservoir materials include polyvinyl chloride, polypropylene, or glass. Product containing particulate matter or having any discoloration should not be administered.

Available dosage forms: Treprostinil is supplied in 20ml ready to use multidose vials in the following concentrations: 1.0 mg/ml, 2.5 mg/ml, 5.0 mg/ml, and 10 mg/ml (no further dilution is necessary).

Sodium Content: Each vial contains 5.3 mg of sodium chloride per ml; however, the 10.0mg/ml strength vial contains 4.0mg of sodium chloride per ml.

Storage: Unopened vials may be used until the labeled expiration date when stored at 15-25°C (59 to 77°F). Temperature excursions are permitted up to 30°C. Opened treprostinil vials should be used for no more than 14 days after the original puncture into the vial. Infusion reservoir cassettes containing treprostinil may be administered up to 72 hours at 37°C.

Monitor: Dyspnea, fatigue, infusion site reactions, and activity tolerance.

Infusion rates may be calculated using the following formula:

Infusion Rate (ml/hr) = **Dose** (ng/kg/min) **x Patient Weight** (kg) **x [(A)*/Treprostinil dosage strength concentration** (mg/ml)**]**

(*Note: (A)=0.00006 for the 1mg/ml, or (A)=0.000024for 2.5mg/ml, or (A)=0.000012 for 5mg/ml, or (A)= 0.000006 for the 10mg/ml concentration)

Click on the hyper link below to access the manufacturer's package insert showing dosing tables 4 through 7 regarding the infusion delivery rates for doses up to 100ng/kg/min, based on the drug delivery rate, concentration and patient weight. Vials are ready to use and require no further dilution prior to administration.

(http://www.unither.com/Remodulin_rev._3-20-02.pdf) accessed 5/20/03

Adverse Effects (Safety Data)[2-4,8]

Table 3 shows those adverse effects that were more common in treprostinil than placebo during controlled studies of patients with pulmonary arterial hypertension. Adverse events occurred at an incidence rate of 3% or more.

Table 3. Adverse Events in Controlled Studies of PAH Patients (with at least a 3% incidence)[3]

Adverse Event	Treprostinil (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Dizziness	9	8
Edema	9	3
Pruritis	8	6
Hypotension	4	2

According to the manufacturer's prescribing information: Adverse events "too general to be informative" were not included, as well as, those "not plausibly attributable to the use of the drug". For instance, those adverse events that can be attributed to the condition being treated (i.e. dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor) or those common in the population being treated were not included (per the manufacturer). Infusion site reactions were defined as any local adverse event other than pain, bleeding or bruising at the infusion site (i.e. erythema, induration, or rash). Infusion site adverse events (reaction and pain) occasionally were severe enough to lead to discontinuation of treatment.

Three episodes of gastrointestinal hemorrhage (2 requiring transfusion) were reported in the literature. Two events were attributed to concomitant administration of an anticoagulant, and one was attributed to NSAID use. These hemorrhagic events resolved upon adjustment of anticoagulation therapy or discontinuation of the NSAID.

Modest reductions in systolic and diastolic blood pressure with an increase in heart rate have been reported in the literature, as well as, symptoms of restlessness.

Table 4. Percentage of Patients reporting Infusion site adverse reactions:[3]

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

Infusion system complications occurred at a rate of 23% with TRE and 33% with Placebo. Side effects causing symptoms of nausea occurred with excess treprostinil infusion and symptoms of PAH (i.e. dyspnea) with insufficient TRE infusion. One hundred and seventy three (93%) pump related problems occurred that necessitated either battery replacement or pump reprogramming. to resolve symptoms of nausea or PAH There were fourteen (7%) infusion set problems that were corrected with syringe replacement or straightening of the crimped infusion line. Side effects associated with the drug delivery system did not lead to clinical instability or rapid deterioration of the patient, neither were there reports of infections in association with the drug delivery system. Side effects were managed by correction of the delivery system pump or infusion set problem.

Overdosage[3]

Seven patients in the controlled clinical trials and seven patients in the open-label follow-on treatment received an overdosage in their medication. Reasons for overdosage included the following: accidental bolus administration of treprostinil, errors in pump program rate of administration, and prescription of an incorrect dose. Overdoses lead to flushing, headache, hypotension, nausea, vomiting, and diarrhea. Reduction in dose or withholding of the treprostinil dose caused these events to be self-limited. Two patients incurred substantial hemodynamic events (hypotension, and near syncope). Supportive treatment should be provided in an overdose situation in addition to reducing or holding the dose of TRE.

Pregnancy[3]

Treprostinil has a Pregnancy Category of B. It should only be used during pregnancy if clearly needed. Studies of pregnant rats did not show evidence of harm to the fetus in regard to organogenesis or late gestational development when continuous subcutaneous infusion rates 117 times the starting human rate or 16 times the average rate on a ng/m^2 basis were used. Studies show that pregnant rabbits incurred an increased incidence of fetal anomalies (bilateral full rib or right rudimentary rib on lumbar 1), which appeared to be related to maternal toxicity (reduced body weight and food consumption). These events occurred at infusion rates that were 41 times the starting rate and five times the average infusion rate used in clinical trials when compared on a ng/m^2 basis.

Labor and Delivery[3]

Effects on labor and delivery are unknown in humans although no effects were seen in animal studies.

Nursing[3]

Caution should be exercised if treprostinil is administered to a nursing woman. It is unknown whether treprostinil is absorbed systemically after ingestion, or whether it is excreted in human milk.

Geriatric Use[3]

Insufficient numbers of patients aged 65 and over have been enrolled in clinical trials; thus, it is unknown whether they respond differently than those younger patients studied to date. If used, dose selection should be cautious due to the increased incidence of decreased hepatic, renal or cardiac function, as well as, concurrent diseases present and concomitant drug therapies encountered in this age group.

Special Populations[3]

Hepatic Insufficiency: Patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency had a 2 to 4 fold respective increase in $C_{max,}$ and these patients had a respective 3 to 5 fold increase in AUC $_{0-\infty}$ compared to healthy subjects who were given a subcutaneous dose of 10 ng/kg/min of Treprostinil for 150 minutes. Patients with hepatic insufficiency showed up to an 80% reduction in clearance as compared to healthy adults. A dose of 0.625 ng/kg/min Ideal Body Weight should be initiated in patients with mild or moderate hepatic insufficiency. Treprostinil has not yet been studied in patients with severe hepatic insufficiency.

Renal Insufficiency: Patients with renal insufficiency have not been studied; therefore, no specific recommendations about dosing can be given. All 5 identifiable metabolites are excreted in the urine, as well as, 4% of the original unchanged dose.

Precautions[2-4,8]

Because treprostinil is a potent pulmonary and systemic vasodilator, initiation of therapy must occur in a setting with experienced clinicians familiar with the diagnosis and treatment of PAH. Adequate personnel and equipment must be available for physiologic monitoring and emergency care as needed. Treprostinil therapy may be used chronically (years), so the patient's ability to administer and care for a subcutaneous catheter and infusion system should be evaluated carefully.

Doses should be increased when there is a lack of improvement or a worsening of PAH symptoms. Additionally, doses should be decreased for excessive pharmacologic effects, or infusion site symptoms that are unacceptable.

Note: There may be a worsening of PAH symptoms should abrupt discontinuation or sudden large reductions in dosage of treprostinil occur.

Pulmonary edema or pulmonary veno-occlusive disease may be exacerbated by TRE.

For additional precautions see those sections regarding pregnancy and breastfeeding, as well as, pediatrics, geriatrics and special populations (renal and hepatic).

Contraindications[3,4,8]

Do not use treprostinil in patients with a known hypersensitivity to the drug or other structurally similar compounds, or any other product ingredient.

Warnings[3,4,8]

Treprostinil is for subcutaneous infusion only.

Drug Interactions[3,4,8]

Additive hypotensive effects may be seen when treprostinil is used with other drugs that alter blood pressure (i.e. diuretics, antihypertensive agents, or vasodilators).

Increased bleeding risks may occur when treprostinil is used with either an anticoagulant/antiplatelet agents or nonsteroidal drugs, as treprostinil inhibits platelet aggregation.

Treprostinil has been used concurrently in clinical trials with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, opiods, corticosteroids and other medications during clinical trials.

Treprostinil did not significantly affect plasma protein binding of normally observed concentrations of digoxin or warfarin during in vitro studies.

Analgesic doses of acetaminophen (1000 mg q6h x 7 doses) did not affect the pharmacokinetics of treprostinil when infused subcutaneously at a rate of 15 ng/kg/min during in vivo studies.

The concomitant use of Treprostonil with either Epoprostenol sodium or Bosentan has not been studied.

Efficacy Measures[3,4,8]

Pulmonary Hypertension

1. Pulmonary Hypertension Lab Parameters
    i. Periodic arterial blood gas monitoring
2. Physical Exam
    i. Periodic pulmonary function tests
    ii. Catheterization and hemodynamic assessments
        1. Pulmonary artery pressure
        2. Pulmonary capillary wedge pressure
        3. Cardiac Index
    iii. Clinical Symptoms
        1. Dyspnea
        2. Fatigue
        3. Edema
        4. Dizziness
        5. Syncope
    iv. Comparison of exercise capacity
        1. Walking distances over time
    v. Quality of Life

Toxicity Measures

1. Lab Parameters
    i. Complete Blood Counts (CBC)
2. Physical Exam
    i. Blood Pressure and Heart Rate
    ii. Infusion site complications/pain
    iii. GI symptoms/diarrhea
    iv. Persistent Headache/jaw pain
    v. Fainting

Clinical Trials[2-4,8-10,11]

Citation	**Simonneau F, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of Treprostinil, a prostacyclin analogue in patients with pulmonary arterial hypertension. American Journal of Respiratory and Critical Care Medicine 2002 Mar 15;165(6):800-4.**
Study Goals	Assess the effects of subcutaneous TRE on exercise capacity, disease symptoms, hemodynamics, and quality of life in patients with pulmonary arterial hypertension
Methods	• **Study Design** ➢ 12 week, multicenter (international), randomized, double-blind, placebo controlled study ➢ N=470 ➢ Written Informed Consent ➢ Approved by local ethics committee at each participating center ➢ Patients received either continuous subcutaneous infusion of treprostinil plus conventional therapy or continuous infusion of placebo (vehicle solution without treprostinil) plus conventional therapy. Conventional therapy was optimized one month before enrollment and included oral vasodilators, oral anticoagulants, diuretics, and/or digitalis. ➢ A permuted block design stratified for baseline exercise capacity and etiology of the patients' PAH was used in the randomization procedure. ➢ Placebo and Treprostinil were administered using a positive pressure microinfusion pump. ➢ Initial dosing started at 1.25 ng/kg/min. Average dose at week 12 was 9.3ng/kg/min. ➢ Doses were increased to a maximum dose where signs and symptoms of pulmonary hypertension improved while maintaining an acceptable side effect profile up to a maximum dose at week 12 of 22.5 ng/kg/min ➢ **Data Analysis** ➢ An intention to treat, nonparametric analysis of covariance was prespecified as the primary analysis when comparing the changes in distances walked in six minutes from baseline to week 12 between treatment groups. ➢ A least squares regression analysis was used to calculate the six-minute walk distances as linear functions of baseline walk, vasodilator use, etiology, and study center. ➢ Next, standardized mid-ranks of the residuals from these linear regression analyses were determined. ➢ The extended Cochran-Mantel-Haenszel test was used to compare the ranks. ➢ The Wilcoxon rank sum test without imputation was used to compare changes from baseline to week 12 in the composite score of signs and symptoms of pulmonary hypertension, Dyspnea-Fatigue Rating, Borg Dyspnea Score and Quality of Life scores. ➢ Parametric analysis of covariance adjusting for baseline value without imputation was used to compare between treatment group changes in hemodynamic variables. ➢ A level of $\alpha = 0.1$ was considered "suggestive of treatment" effect in the analysis of possible treatment interactions by the authors.
Criteria	• **Inclusion criteria** ➢ Primary pulmonary hypertension or pulmonary hypertension associated with connective tissue diseases or associated with congenital systemic to pulmonary shunts ➢ Age 8-75 years old ➢ PAH with New York Heart Association functional class II, III, or IV ➢ Significant pulmonary hypertension as defined by: Mean pulmonary arterial pressure ≥ 25mm Hg at rest

Mean pulmonary capillary wedge pressure ≤ 15mm Hg
Pulmonary vascular resistance > 3 mm Hg/L/min

- Ventilation perfusion lung scan or pulmonary angiography not indicative of thromboembolic disease

- **Exclusion criteria**
  - Significant parenchymal pulmonary disease as evidenced by pulmonary function tests or high resolution CT scan
  - Porto-pulmonary hypertension or HIV-associated pulmonary hypertension
  - Uncontrolled sleep apnea
  - History of left sided heart disease
  - Other diseases associated with pulmonary hypertension (i.e. sickle cell anemia, shistosomiasis)
  - Baseline exercise capacity of less than 50 m or greater than 450 m walked in 6 min
  - Any new type of chronic therapy for pulmonary hypertension added within the last month
  - Any pulmonary hypertension medication discontinued within the last week except anticoagulants
  - Any use of prostaglandin derivatives within the past 30 days

Results

Patients were well matched for baseline demographic and hemodynamic characteristics of the two groups as shown in tables 1 and 2 below. Patients were also well matched with respect to severity of pulmonary hypertension, duration of illness and etiology of illness.

Table 1. Patient Demographics at Baseline:

Characteristic	Treprostinil	Placebo
Age, yr	44.6 ± 1.0	44.4 ± 0.9
Sex, n (%)		
Male	36(16)	51(22)
Female	197(85)	185(78)
Ethnic Group, n (%)		
Black	13(6)	8(3)
White	198(85)	198(85)
Other	22(9)	30(13)
NYHA functional class, n		
II	25(11)	28(12)
III	190(82)	192(81)
IV	18(8)	16(7)
6 minute walk distance,	326 ± 5	327 ± 6
Etiology of pulmonary		
Primary pulmonary	134(58)	136(58)
Connective Tissue	41(17)	49(20)
Congenital systemic to	58(25)	51(22)
Years since pulmonary	4.3 ± 0. 5	3.3 ± 0.5

Table 2. Baseline Hemodynamic Variables:

	(N=233)	(N=236)*
Heart Rate, beats/min	82 ± 1	82 ± 1
Mean right atrial pressure, mm Hg	10 ± 0.4	10 ± 1
Mean pulmonary artery pressure, mmHg	62 ± 1	60 ± 1
Mean pulmonary capillary wedge pressure, mmHg	10 ± 0.3	9 ± 0.2
Cardiac Index, L/min/m^2	2.4 ± 0.1	2.3 ± 0.1
Pulmonary vascular resistance index, units/ m^2	26 ± 1	25 ± 1
Mean systemic artery pressure, mm Hg	90 ± 1	91 ± 1
Systemic vascular resistance Index, units/m^2	38 ± 1	39 ± 1
Mixed venous oxygen saturation, %	62 ± 1	60 ± 1
Arterial oxygen saturation	92 ± 0.5	91 ± 0.5

*One Placebo patient did not receive any study drug; thus that patient's results were not included in the analysis of the primary endpoints.

Data analysis:
Exercise capacity improved with TRE, but was unchanged with placebo by week 12. The between group difference in the median distance walked in 6 minutes was 16 meters, and it was stated to be statistically significant by the authors.

Between Group Difference at Week 12	Median Distance Walked	95%CI	p-value
Distance Walked in 6 Minutes	16 meters	4.4-27.6m	p=0.006

Baseline demographic covariates and disease etiology showed no significant interaction with the change in exercise capacity. A treatment interaction was observed with the baseline walking distance (p=0.03), baseline NYHA functional class (p=0.11), and baseline mixed venous oxygen saturation (p=0.07). The more compromised the patient at baseline the greater the improvement in exercise capacity at week 12. Severely ill patients who walked less than 150m at baseline walked +51 ± 16m (p=0.002).

Additionally there was a relationship proposed between the *dose* of TRE achieved by week 12 and the change in the 6-minute walk distance. When patients were grouped by quartile, the highest dose quartile had the greatest improvement in the 6-minute walk distance (table 3).

Table 3. Mean change in 6 min walk distance

Quartile	Dose (ng/kg/min)	Mean change in 6 min walk distance from baseline to Week 12 versus Week 12 Treprostonil dose quartile
1	< 5.0	+33±10m
2	5.0 to <8.2	+14±9m
3	8.2 to <13.8	+20±8m
4	>13.8	+36.1±10m

Signs and Symptoms Composite Score of Pulmonary Arterial Hypertension significantly improved in the Treprostinil group, but worsened in the Placebo group (table 4).

Table 4. Signs and Symptoms Composite Score of Pulmonary Arterial Hypertension

Group	Baseline	Week 12
Treprostonil	7.6 ±0.5	8.5±0.5
Placebo	7.5±0.4	7.4±0.2
Between group comparison:		P<0.0001

Dyspnea-Fatigue Rating significantly improved in TRE group & worsened in the Placebo group.

Table 5. Dyspnea-Fatigue Rating

Group	Baseline	Week 12
Treprostinil	4.2±0.1	5.4±0.2
Placebo	4.4±0.1	4.3±0.1
Between group comparison:		P=0.0001

Gastrointestinal hemorrhage with melena occurred in 3 of the TRE treatment group patients, and none of the placebo patients. Two patients with hemorrhage had "excessively" increased INR of 4.0 & 3.14. One patient had used naproxen. All three events subsided spontaneously and the authors suggest that no clinically adverse consequences occurred, although two patients required transfusion of packed red blood cells.

Clinical deterioration and deaths occurred in both the Treprostinil group and Placebo group. This occurred both while patients were receiving study drug and after withdrawal of the study drug during the 12 week study.

Table 7. Deaths, transplantations and Clinical Deterioration.

Adverse events:	Total Patients	Treprostinil	Placebo
Death while receiving study drug	14	7	7
Death after withdrawal of study drug during the 12 week study	5	2	3
Transplantation	1	0	1

	Clinical Deterioration	12	6	6
Author's Conclusions	Chronic subcutaneous infusions of Treprostinil are effective treatments with an acceptable safety profile for patients with pulmonary arterial hypertension.			
Critique	• **Strengths** -Prospective, double blind, randomized placebo-controlled trial -Trial was appropriately powered to detect a difference from Placebo. • **Limitations** -Manufacturer supported research. -United Therapeutics Corporation -Primary endpoints were not published or discussed by the authors. A 55 meter increment in a 6 minute walk, and a trend toward reduced mortality or need for transplantation after treatment with TRE were discussed in the FDA's report from the Cardiovascular and Renal Drugs Advisory Committee's review of this pivotal trial. -81% of patients studied were female. (VA population is primarily male). -Mean age of 45yo in the study. (VA population typically older). -A short 12 week trial makes it difficult to fully assess side effects, adverse reactions, and harm. The maximum effective dose was never determined. -Infusion site pain, swelling and erythema may have unblinded the study to both the participants and observers. -Questions arise regarding the ethics of the trial, as the placebo arm was denied the known standard of care for 12 weeks. The mean life expectancy is 2.8 years when patients are left untreated. - It is unknown as to what impact the different types of conventional therapy may or may not have had on the study results. The authors do not adequately describe what "optimization of conventional therapy" means in regard to this study. -Sample populations receiving anticoagulant and/or non-steroidal therapy are not adequately described. -Authors state that INRs of 3.14 and 4.0 were "excessively high. No information is available regarding acceptable INR target ranges, about how well these INR elevations were tolerated in other study participants, or how frequently they occurred. Did TRE potentiate INR's? -No arm to compare TRE with "gold standard" PGI2 to make a head to head comparison. -FDA reviewers suggest that flaws were introduced in the statistical analysis of exercise improvement by pooling of the study data. There were 2 trials whose data were pooled. -A significance level of $\alpha = 0.1$ was accepted as being "suggestive" of a treatment effect when a level of $\alpha = 0.05$ is generally required to demonstrate a statistically significant effect. -The degree of heart failure at time of randomization may have impacted the outcome of the study. -Frequency of study discontinuation due to infusion site pain or infusion site reaction, and the use of analgesics to treat infusion site pain may have impacted the outcome of this study. -Analgesic use was highest in the Treprostonil treated group. Analgesics may have altered vascular dynamics or mitigated pain associated with pulmonary artery hypertension. -Study not designed to assess effects on number of hospitalizations or effects on mortality. -No statistics reported regarding gastrointestinal hemorrhagic events due to either anticoagulant use or non-steroidal use.			

<table>
<tr><td>Citation
Abstract</td><td>Barst RJ, Horn EM, Widlitz CA et al. Efficacy of Long term subcutaneous Infusion of UT-15 (TRE) in Primary Pulmonary Hypertension. European Heart Journal. 2000;21:315 Abstract.</td></tr>
<tr><td>Study Goals</td><td>Determine the safety and efficacy of chronic UT-15 therapy in Primary Pulmonary Hypertension.</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Efficacy measures included baseline and follow-up six-minute walk distances, hemodynamics and NYHA functional class.</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Patients with Primary Pulmonary Hypertension.
➢ Male or female patients
➢ 12-71year old patients
• Exclusion criteria
➢ None described</td></tr>
<tr><td>Results</td><td>Eleven female and 3 male patients with mean age of 33±18 years, range 12 to 71 years) were treated with long term UT-15.

Reasons for Discontinuation of Therapy during study:
<table>
<tr><th>Reason for discontinuation of UT-15</th><th># of Patients discontinuing therapy</th></tr>
<tr><td>Inability to achieve a tolerable dose (Reason: Limited available drug concentrations & limitations of infusion pump)</td><td>1</td></tr>
<tr><td>Intolerable pain at infusion site</td><td>2</td></tr>
<tr><td>Clinical Deterioration</td><td>3</td></tr>
</table>
Eight of the eleven remaining patients were treated for 12.0±0.5 months (range 11-16 months).
<table>
<tr><th></th><th>Distance (m)</th><th>New York Heart Association Functional Class</th><th>Pulmonary Arterial Pressure (mmHg)</th><th>Cardiac Index (L/min/m²)</th><th>Peripheral Vascular Resistance (units m²)</th></tr>
<tr><td>Baseline</td><td>430±37</td><td>3.0±0.0</td><td>61±7</td><td>3.2±0.3</td><td>19±3</td></tr>
<tr><td>Follow-up</td><td>510±49</td><td>2.4±0.2</td><td>63±7</td><td>3.6±0.4</td><td>17±3</td></tr>
<tr><td>P Value</td><td>0.04</td><td>0.06</td><td>NS</td><td>NS</td><td>NS</td></tr>
</table></td></tr>
<tr><td>Authors' Conclusions</td><td>UT-15 can be safely administered via subcutaneous infusion in patients with PPH with favorable effects on exercise capacity during the first year of treatment.</td></tr>
<tr><td>Critique</td><td>• Strengths
➢ Insufficient information available upon which to critique
• Limitations
➢ Sample size too small to reach any conclusions.</td></tr>
</table>

<table>
<tr><td>Citation</td><td>Lazaro M, Escibano P, Pombo M et al. Continuous Subcutaneous Infusion of UT-15(TRE) (Stable Prostacyclin Analogue) in Severe Pulmonary Hypertension: Long Term Outcome. European Heart Journal. 2001</td></tr>
<tr><td>Study Goals</td><td>Objectives: Evaluation of functional class, exercise capacity, and hemodynamic profile after 6 & 12 months of treatment with TRE.</td></tr>
<tr><td>Methods</td><td>• Study Design
Open label international study</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Patients with severe pulmonary arterial hypertension
➢ Male and female patients
• Exclusion criteria
➢ Unknown due to abstract presentation of study information</td></tr>
<tr><td>Results</td><td>• Twenty patients enrolled (13 women & 7 men)
• Mean age of 44.9±13.9
• 7 patients with Primary pulmonary hypertension
• 5 patients with Pulmonary Hypertension due to Toxic Oil Syndrome
• 1 Patient with HIV
• 1 Patient with anorexigens use
• 2 Patients with connective tissue disease
• 3 patients with congenital heart disease
• 1 Non-surgical thromboembolic Pulmonary Hypertension

Efficacy Measure
Right heart catheterization performed at baseline and after, at least 12 months of therapy. Every 6 months the patients functional class and 6 minute walk test were evaluated. Mean follow-up was 14.4 months with a range of 8-21 months.

<table>
<tr><th></th><th>Baseline</th><th>6 months (n=20)</th><th>p-value*</th><th>≥12 months (n=14)</th><th>p-value*</th></tr>
<tr><td>PAPm</td><td>56.2±15.1</td><td>-</td><td></td><td>50.1±11.5</td><td>NS</td></tr>
<tr><td>CO</td><td>4.0±1.3</td><td>-</td><td></td><td>4.1±1.3</td><td>NS</td></tr>
<tr><td>O2AP</td><td>57.9±11.9</td><td>-</td><td></td><td>60.7±12.3</td><td>NS</td></tr>
<tr><td>6 min walk</td><td>343±67</td><td>371±74</td><td>NS</td><td>386±49</td><td>0.01</td></tr>
<tr><td>NYHA</td><td>3.0±0.3</td><td>2.7±0.6</td><td>NS</td><td>2.6±0.5</td><td>0.01</td></tr>
<tr><td>UT-15 (TRE) Dose</td><td>0</td><td>8.5±2.4</td><td></td><td>14.6±2.5</td><td></td></tr>
</table>
PAPm=Mean Pulmonary Arterial Pressure (mmHg); CO= Cardiac Output (1pm); O2AP=Oxygen Pulmonary Artery Saturation (%); 6 min Walk (meters); UT-15 Doses (ng/kg/min). *p-value relative to baseline.</td></tr>
<tr><td>Arthors' Conclusions</td><td>UT-15 subcutaneous continuous infusions improve functional class and exercise capacity in patients with severe PH. This improvement is dependent upon UT-15 dosage. Subcutaneous infusions of UT-15 are safe and effective for the treatment of PH with the delivery problems of intravenous prostacyclin.</td></tr>
<tr><td>Critique</td><td>• Strengths
➢ Long term outcomes with UT-15 described
• Limitations
➢ Abstract presentation of study information
➢ Change in baseline over 2 months could potentially be attributable to various factors and therapies that are inadequately described in the abstract.</td></tr>
</table>

Acquisition Costs

Drug	Dose	Cost/Vial
Treprostinil	1mg vials	$1,300.00/vial
(prices off. 5/22/2002)	2.5mg vials	$3,250.00/vial
	5mg vials	$6,500.00/vial
	10mg vials	$7,800.00/vial
	Sof-sorter Inf. Set	$63.70/system
	Batteries 1.5v	$2.43/sheet
	Mini-Med 42" tubing	$9.19 each
	Mini-Med 3ml syringe reservoir	$3.41 each
PGI2prostinil	0.5mg vials	$19.01/vial
(prices off. 9/15/02)	1.5mg vials	$39.91/vial
	Diluent	$11.99/vial
	50ml cassettes	$13.92/cassette
	100ml cassettes	$20.00/cassette
	Extension tubing sets	$3.24/set

Cost Analysis

To date no cost-effectiveness trials have been conducted between Epoprostenol and TRE. Nor have dose equivalency studies been described in the literature to aid in comparing costs between these agents.

Data Compilation Tables

Calculation of a number needed is not applicable as the published research is not outcomes based.

Conclusions[9-10]

Optimal treatment for PAH remains to be fully described as on going clinical studies with TRE are published. Head to head trials with therapeutic options are needed to fully elucidate the benefits of one agent over another. TRE was approved by the FDA's advisory Committee because of "recognized poor clinical outcomes" in patients with PAH, and because the "complications and logistical problems" associated with Epoprostenol at the time of approval. Thus, the FDA's committee used a more liberal approach that allowed for the recommendation of approval of TRE onto the market by a 6 to 3 margin of vote.

TRE approval was based on improvement in "perceived" quality of life, dyspnea score and reduction in other symptoms such as syncope and fatigue, as well as, a lack of safety concerns. TRE is the only FDA approved product for treating NYHA II PAH. TRE is also approved for NYHA class III & IV as is PGI2. Similar adverse effects occur with both TRE and PGI2. NYHA III & IV patients should try PGI2 first, and then TRE in the event that problematic infusion site or infusion delivery problems arise that cannot be reconciled.

Recommendations[2-5,8,10,13-14]

According to the manufacturer of PGI2, the risks of therapy with PGI2 outweigh the benefits for NYHA class I patients. TRE is not yet FDA approved for NYHA class I. Therefore, NYHA class I patients should be given traditional therapy with oral agents such as anticoagulants, diuretics, digoxin and vasodilators (such as Diltiazem).

Because improved survival has not yet been adequately described in NYHA class II patients on TRE, it is recommended that a trial of PGI2 be tried initially. If the patient cannot tolerate or manage centrally administered PGI2, then therapy with TRE may be indicated as a viable option in this patient population.

Because PGI2 has been extensively studied and because there is supporting evidence of improved survival when used long term in patients with severe symptomotology. It is recommended that NYHA class III & IV patients be treated first line with conventional oral therapies such as oral vasodilators, oral anticoagulants, diuretics, and/or digitalis and then with PGI2.

It is recommended that Treprostinil have a non-formulary classification, and only be allowed after failure (ie: sepsis, delivery system complications with recurrent and/or emergent symptomotology of PAH,) with PGI2 therapy for NYHA class II-IV patients in order to avoid interruptions in prostacyclin therapy or costly hospitalizations to treat sepsis.

References:

1. Galie N, Torbreki A. Pulmonary arterial hypertension: new ideas and perspectives. Heart 2001;85:475-80.
2. Chattaraj SC. Treprostonil sodium Pharmacia. Curr Opin Investig. Drugs. 2002 Apr;3(4):582-6.
3. United Therapeutics Corporation, Remodulin package insert. Research Triangle Park, NC: 2002, March.
4. DRUGDEX Editorial Staff. Thomson Micromedex, Treprostinil. (http://healthcare.micromedex.com/mdxcgi/display.exe?CTL=/u01/mdx/mdxcgi/MEGAT.SYS&), accessed 3 February 2003.
5. GlaxoSmithKline, Flolan package insert. Research Triangle Park, NC:2001, July.
6. Mohler ER, Klugherz B, Goldman R et all: Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication. Vasc Med 2000; 5:231-7.
7. Clapp LH, Finney P, Turato S: Antiproliferative and Cyclic-AMP elevating properties of stable prostacyclin analogue in human pulmonary artery smooth muscle. Abstract presented at ATS 97th International Conference. San Francisco, CA: May, 2001.
8. Cada DJ, Levien T, Baker DE. Treprostinil Sodium Injection Hosp Pharmacy 2002, Nov;37(11):1196-1202.
9. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo controlled trial. Am J Resp Crit Care Med. 2002 Mar 15; 165(6):800-4.
10. Fleming T,Lindenfeld J, Lipicky R, et al: Report from the 93rd Cardiovascular and Renal Drugs Advisory Committee Meeting, August 9-10,2001. Circulation 2001, Oct 9;104(15):1742. Report.
11. Barst RJ, Horn EM, Widlitz CA et al. Efficacy of Long term subcutaneous Infusion of UT-15 (TRE) in Primary Pulmonary Hypertension. European Heart Journal. 2000;21:315 Abstract.
12. Lazaro M, Escibano P, Pombo M et al. Continuous Subcutaneous Infusion of UT-15 (TRE) (Stable Prostacyclin Analogue) in Severe Pulmonary Hypertension: Long Term Outcome. European Heart Journal. 2001. Abstract.
13. Galie N, Branzi A. Medical therapy of pulmonary hypertension. The prostacyclins. Clin Chest Med. 2001 Sep;22(3):529-37.
14. Pass S, Dusing M. Current and emerging therapy for primary pulmonary hypertension. Ann Pharmacother. 2002 Sep;36(9):1414-23.

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Date: 6-15-03

Executive Summary

Introduction:

Treprostinil Sodium is a prostacyclin analogue indicated for the treatment of Pulmonary Arterial Hypertension (PAH). It is the first approved therapy for patients with New York Heart Class II PAH, and it may also be used for the treatment of other symptomatic stages of the disease Class III-IV. Studies show that Treprostinil can improve exercise capacity, dyspnea scores during exercise, hemodynamics, and quality of life. Treprostinil has been used for up to 4 years in patients participating in clinical trials. Treprostinil's exact place in therapy will be delineated with further studies.

Treprostinil's advantage over its predecessor (Epoprostenol (PGI2)) is that it may help reduce life-threatening complication rates associated with the central venous administration requirement of PGI2. Central venous therapy with PGI2 carries the risk of sepsis, catheter related embolism, thrombosis, and delivery system malfunctions such as accidental occlusions, perforations and dislodgments of the catheter, as well as, pump malfunction. *Any* interruption in therapy may be associated with syncope and death from an acute pulmonary hypertensive crisis due to the short half-life (1-2 minutes) of PGI2. Pharmacokinetic advantages of Treprostinil include its longer half-life (3-4 hours) and subcutaneous route of administration. Reconstitution and/or refrigeration are not required during Treprostinil administration as they are with PGI2. Infusion site erythema, swelling and pain have occurred with Treprostinil treatment and have occasionally been severe enough to require discontinuation of therapy.

Treatment:

Treatment for PAH should begin with traditional oral vasodilators; however if oral agents alone fail then parenteral options may be added or substituted. Neither Epoprostenol nor Treprostinil are approved for NYHA Class I. Only Treprostinil is approved for treatment of NYHA Class II PAH. Because Epoprostenol has been shown to improve symptoms of PAH, improve survival and delay the need for lung transplantation, it should be used prior to initiating therapy with Treprostinil for NYHA classes III & IV.

Vasodilator Algorithm: