United Therapeutics CORPORATION

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August 25, 2015

Diahann Wilcox, APRN
University of Connecticut Health Center
263 Farmington Avenue
Farmington, CT 06030

Reference No.: US15-000926

Dear Ms. Wilcox:

Your August 25, 2015 request for information regarding transitioning patients from Remodulin® (treprostinil) Injection to Orenitram™ (treprostinil) Extended-Release Tablets and transitioning patients from Orenitram to a temporary infusion of Remodulin has been forwarded to us by your United Therapeutics Medical Science Liaison, Bhavisha Desai. If you are receiving this letter in error and did not initiate an inquiry for this information, please call United Therapeutics Corp.'s Global Medical Information department at 877.522.2950. Information addressing your inquiry is provided herein.

ORENITRAM™ (treprostinil) Extended-Release Tablets

INDICATION
Orenitram is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).

When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

IMPORTANT SAFETY INFORMATION for Orenitram
CONTRAINDICATIONS
- Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

WARNINGS AND PRECAUTIONS

- Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
- Orenitram inhibits platelet aggregation and increases the risk of bleeding
- Orenitram should not be taken with alcohol as release of treprostinil from the tablet may occur at a faster rate than intended
- The Orenitram tablet shell does not dissolve. In patients with diverticulosis (blind-end pouches), Orenitram tablets can lodge in a diverticulum

DRUG INTERACTIONS / SPECIFIC POPULATIONS

- Concomitant administration of Orenitram with diuretics, antihypertensive agents, or other vasodilators increases the risk of symptomatic hypotension
- Orenitram inhibits platelet aggregation; there is an increased risk of bleeding, particularly among patients receiving anticoagulants
- Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil; therefore, Orenitram dosage reduction may be necessary in these patients
- Pregnancy Category C. Animal reproductive studies with Orenitram have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans.
- Safety and effectiveness in patients under 18 years of age have not been established
- There is a marked increase in the systemic exposure to treprostinil in hepatically impaired patients

ADVERSE REACTIONS

- In the 12-week placebo-controlled monotherapy study, adverse reactions with rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity, hypokalemia, and abdominal discomfort

Please see accompanying full Prescribing Information and Patient Information for more information on Orenitram.

I hope that you find this information helpful. If you have any questions regarding this letter, you may contact United Therapeutics Corp.'s Global Medical Information department at 877.522.2950. Thank you for your inquiry and interest in Orenitram.

Kind Regards,

Elizabeth O. Herman, PharmD, MS
Medical Information Scientist, Global Medical Information
Office: 919.425.5508
Fax: 919.485.8352

Enclosure: Orenitram Full Prescribing Information - Oct 2014
Orenitram Patient Information - Oct 2014

TEMPORARY TRANSITION FROM ORENITRAM™ (TREPROSTINIL) EXTENDED-RELEASE TABLETS TO REMODULIN® (TREPROSTINIL) INJECTION

INDICATIONS AND USAGE

Oral treprostinil is approved in the United States (US) under the name of Orenitram for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve exercise capacity. [Orenitram USPI] The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). [Jing, 2013] When used as the sole vasodilator, the effect of oral treprostinil on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Oral treprostinil is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

Treprostinil injection is approved in the US under the name of Remodulin for the treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise. [Remodulin USPI] Studies establishing effectiveness included patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). [Remodulin USPI; Simonneau, 2002] Treprostinil may be administered as a continuous subcutaneous (SC) infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous IV infusion should be reserved for patients who are intolerant of the SC route, or in whom these risks are considered warranted.

TEMPORARY TRANSITION FROM ORAL TO SC/IV TREPROSTINIL

United Therapeutics Corporation has not conducted a prospective controlled clinical trial evaluating the optimal method of transitioning patients with PAH from oral treprostinil to a temporary infusion of SC/IV treprostinil and back to oral treprostinil. Very limited data are available from a retrospective analysis of ten patients that required transition from oral treprostinil to SC/IV treprostinil during a Phase III, open-label extension study in patients with PAH (FREEDOM-EXT). [Nathan, 2013] These data, as well as pharmacokinetic and dosing considerations, are discussed herein.

PHARMACOKINETIC AND DOSING CONSIDERATIONS

Treprostinil is a chemically stable prostacyclin analogue approved in the US for SC/IV (as Remodulin), inhaled (as Tyvaso®), and oral (as Orenitram) administration. In the plasma at physiological pH, both the treprostinil sodium (SC/IV and inhaled treprostinil formulations) and treprostinil diolamine (oral treprostinil) salts disassociate from their respective salt counterions and exist as the freely ionized form of treprostinil.

As stated in the oral treprostinil prescribing information, a temporary infusion of SC/IV treprostinil may be considered in the event of planned, short-term treatment interruption for patients unable to take oral medications. [Orenitram USPI] The following equation can be used to estimate an equivalent dose of SC/IV treprostinil in ng/kg/min when a patient's total daily dose of oral treprostinil (in mg) and the weight (in kg) are available:

$$\text{SC or IV treprostinil dose in ng/kg/min} = \frac{\text{X mg}}{\text{1 day}} \times \frac{1}{5} \times \frac{\text{1,000,000 ng}}{\text{1 mg}} \times \frac{\text{1 day}}{\text{1,440 min}} \times \frac{1}{\text{patient's weight in kg}}$$

- X mg = total daily dose of oral treprostinil in mg
- $\frac{1}{5}$ = bioavailability factor (rounded from 17%, the absolute bioavailability of oral treprostinil [Orenitram USPI])

Example calculation for a 70-kg patient receiving oral treprostinil 3 mg twice daily (BID) or 2 mg three times daily (TID):

$$\frac{\text{6 mg}}{\text{1 day}} \times \frac{1}{5} \times \frac{\text{1,000,000 ng}}{\text{1 mg}} \times \frac{\text{1 day}}{\text{1,440 min}} \times \frac{1}{\text{70 kg}} = \text{11.90 ng/kg/min SC or IV treprostinil}$$

A reference table for estimating an equivalent dose of SC/IV treprostinil is provided at the conclusion of this letter (Table 2). Please note that this table is derived from the aforementioned equation and results in an estimation of a potential equivalent dose of SC/IV treprostinil (in ng/kg/min), based on a patient's total daily dose of oral treprostinil (in mg) and weight (in kg). This table does not provide precise equivalent doses, and may result in an estimated equivalent dose range. A patient's dose of SC/IV treprostinil may differ from estimations; treprostinil dosing is to be individualized according to clinical response. [Orenitram USPI; Remodulin USPI]

When discontinuing oral treprostinil, reduce the dose in increments of 0.5 to 1 mg per day. [Orenitram USPI] Do not abruptly discontinue oral treprostinil. Abrupt discontinuation or

sudden large reductions in dosage of oral treprostinil may result in worsening of PAH symptoms. Consideration should be given to up-titrating the SC/IV treprostinil dose based on the patient's clinical response and according to the prescribing information. [Remodulin USPI] The patient should be closely monitored for excessive pharmacologic effects of treprostinil (headache, nausea, emesis, etc.). Factors including the dose of oral treprostinil, how well oral treprostinil is tolerated, and the stability of the patient should also be considered before initiating this temporary transition.

The patient should be slowly transitioned back to the previous dose of oral treprostinil by up-titrating the oral treprostinil dose while down-titrating the SC/IV treprostinil dose. Again, the patient's care plan should include close monitoring for excessive pharmacologic effects of treprostinil. In a recently completed 24-week, open-label study, patients on a stable dose of SC/IV treprostinil (receiving SC/IV treprostinil for ≥ 90 days and without a prescribed dose change for ≥ 30 days) were transitioned to oral treprostinil. [http://clinicaltrials.gov/show/NCT01588405] Patients began the transition in the hospital and the target in-hospital time frame for a complete transition was five days; however, the transition may have been extended beyond five days if necessary for patient safety. [data on file] Oral treprostinil was initiated with twice daily (BID) or three time daily (TID) dosing. The dose of SC/IV treprostinil was decreased as the dose of oral treprostinil was increased over the five days. Oral treprostinil was not increased more than 2 mg TID within a 24-hour period and SC/IV treprostinil was not decreased more than 30 ng/kg/min within a 24-hour period. If needed, SC/IV treprostinil dose was adjusted more than TID. Preliminary results of this study, including data from 33 enrolled patients, are available [White, 2014] and final results are expected to be published in 2015.

RETROSPECTIVE REVIEW OF ORAL TREPROSTINIL CLINICAL TRIAL PATIENTS

Nathan et al. conducted a retrospective review of patients enrolled in the open-label FREEDOM-EXT extension study [White, 2013] and reported data from ten patients who required transition to SC/IV treprostinil from oral treprostinil (seven due to worsening PAH symptoms and three for abdominal surgery that required temporary nothing-by-mouth [NPO] status). [Nathan, 2013] Five patients (50%) transitioned to IV treprostinil and five transitioned to SC treprostinil. Results are as follows:

- Mean oral treprostinil dose before transition: 7.7 mg BID (range: 3.5-21 mg BID)
- Mean starting dose of SC/IV treprostinil: 9.5 ng/kg/min (range: 2-20 ng/kg/min)
- Mean conversion time: 4.75 days (range: 2-8 days)
- Mean final dose of SC/IV treprostinil: 45.3 ng/kg/min (range:17-90 ng/kg/min)
- Mean final daily SC/IV to oral treprostinil dose ratio: 7 ng/kg/min to 1 mg BID (range: 2.5-10 ng/kg/min to 1 mg BID)

There were no patients who required the transition to be aborted and there were no documented episodes of hemodynamic decompensation or increased PAH symptoms. One patient experienced adverse events during the switch (hypotension, nausea, and loose stools). Four patients (three recovering from abdominal surgery) were subsequently transitioned back to oral treprostinil. As this was a retrospective review, there was no protocol for transitions in place; transitions were performed at the discretion of the principal investigators at each center. An

example patient transition case from this report is provided in Table 1. The patient's transition to SC treprostinil was initiated in a step-down unit and completed in a cardiovascular intensive care unit for close monitoring. No right heart catheterization was performed prior to the patient being discharged home after eight days.

Table 1: Example Patient Transition

Day	Oral Treprostinil Dosing	SC Treprostinil Dosing	Comments
1	8 mg BID	None	-
2	8 mg AM/7 mg PM	5 ng/kg/min (7 hrs after AM dose)	-
3	6 mg AM/5 mg PM	10 ng/kg/min (7 hrs after AM dose)	Nausea/BP drop; rec'd fluid bolus
4	4 mg AM/3 mg PM	15 ng/kg/min (7 hrs after AM dose)	SOB improved; nausea improved
5	2 mg AM/1 mg PM	20 ng/kg/min (7 hrs after AM dose)	Loose stools; BP drop
6	None	20 ng/kg/min (7 hrs after AM dose)	Loose stools; SOB improved
7	None	20 ng/kg/min (7 hrs after AM dose)	Hypotensive and nauseated; DC'd metoprolol and decreased sildenafil to 20 mg TID

AM: morning; BID: twice daily; BP: blood pressure; DC'd: discontinued; hrs: hours; PM: evening; rec'd: received; SOB: shortness of breath; TID: three times daily
Adapted from: Nathan, 2013

Nathan et al. concluded that patients may be safely transitioned from oral to SC/IV treprostinil, but the optimal dose-to-dose equivalence and treatment overlap strategies remain to be determined and should be individualized.

Table 2. Reference Table for Estimating an Equivalent Subcutaneous/Intravenous Treprostinil Dose (ng/kg/min) from a Total Daily Dose of Oral Treprostinil (mg) and Patient Weight (kg)

Patient Weight (kg)	Total Daily Oral Treprostinil Dose (mg)																		Subcutaneous/Intravenous Treprostinil Dose (ng/kg/min)
	1	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	
40	3.47	6.94	13.89	20.83	27.78	34.72	41.67	48.61	55.56	62.50	69.44	76.39	83.33	90.28	97.22	104.17	111.11	118.06	125.00	
45	3.09	6.17	12.35	18.52	24.69	30.86	37.04	43.21	49.38	55.56	61.73	67.90	74.07	80.25	86.42	92.59	98.77	104.94	111.11	
50	2.78	5.56	11.11	16.67	22.22	27.78	33.33	38.89	44.44	50.00	55.56	61.11	66.67	72.22	77.78	83.33	88.89	94.44	100.00	
55	2.53	5.05	10.10	15.15	20.20	25.25	30.30	35.35	40.40	45.45	50.51	55.56	60.61	65.66	70.71	75.76	80.81	85.86	90.91	
60	2.31	4.63	9.26	13.89	18.52	23.15	27.78	32.41	37.04	41.67	46.30	50.93	55.56	60.19	64.81	69.44	74.07	78.70	83.33	
65	2.14	4.27	8.55	12.82	17.09	21.37	25.64	29.91	34.19	38.46	42.74	47.01	51.28	55.56	59.83	64.10	68.38	72.65	76.92	
70	1.98	3.97	7.94	11.90	15.87	19.84	23.81	27.78	31.75	35.71	39.68	43.65	47.62	51.59	55.56	59.52	63.49	67.46	71.43	
75	1.85	3.70	7.41	11.11	14.81	18.52	22.22	25.93	29.63	33.33	37.04	40.74	44.44	48.15	51.85	55.56	59.26	62.96	66.67	
80	1.74	3.47	6.94	10.42	13.89	17.36	20.83	24.31	27.78	31.25	34.72	38.19	41.67	45.14	48.61	52.08	55.56	59.03	62.50	
85	1.63	3.27	6.54	9.80	13.07	16.34	19.61	22.88	26.14	29.41	32.68	35.95	39.22	42.48	45.75	49.02	52.29	55.56	58.82	
90	1.54	3.09	6.17	9.26	12.35	15.43	18.52	21.60	24.69	27.78	30.86	33.95	37.04	40.12	43.21	46.30	49.38	52.47	55.56	
95	1.46	2.92	5.85	8.77	11.70	14.62	17.54	20.47	23.39	26.32	29.24	32.16	35.09	38.01	40.94	43.86	46.78	49.71	52.63	
100	1.39	2.78	5.56	8.33	11.11	13.89	16.67	19.44	22.22	25.00	27.78	30.56	33.33	36.11	38.89	41.67	44.44	47.22	50.00	
105	1.32	2.65	5.29	7.94	10.58	13.23	15.87	18.52	21.16	23.81	26.46	29.10	31.75	34.39	37.04	39.68	42.33	44.97	47.62	
110	1.26	2.53	5.05	7.58	10.10	12.63	15.15	17.68	20.20	22.73	25.25	27.78	30.30	32.83	35.35	37.88	40.40	42.93	45.45	
115	1.21	2.42	4.83	7.25	9.66	12.08	14.49	16.91	19.32	21.74	24.15	26.57	28.99	31.40	33.82	36.23	38.65	41.06	43.48	
120	1.16	2.31	4.63	6.94	9.26	11.57	13.89	16.20	18.52	20.83	23.15	25.46	27.78	30.09	32.41	34.72	37.04	39.35	41.67	
125	1.11	2.22	4.44	6.67	8.89	11.11	13.33	15.56	17.78	20.00	22.22	24.44	26.67	28.89	31.11	33.33	35.56	37.78	40.00	

- Example estimation 1: Based on the above table, an estimated equivalent dose of SC/IV treprostinil for a 70-kg patient receiving 12 mg oral treprostinil daily is 23.81 ng/kg/min (row '70' x column '12' = 23.81 ng/kg/min SC/IV treprostinil).
- Example estimation 2: Based on the above table, an estimated equivalent dose of SC/IV treprostinil for a 83.25-kg patient receiving 18 mg oral treprostinil daily is between 29.41 – 31.25 ng/kg/min (rows '80' and '85' x column '18' = 31.25 and 29.41 ng/kg/min, respectively).
- Example estimation 3: Based on the above table, an estimated equivalent dose of SC/IV treprostinil for a 68-kg patient receiving 21 mg oral treprostinil daily is between 39.68 – 47.01 ng/kg/min (rows '65' and '70' x columns '20' and '22' = 42.74 and 39.68 and 47.01 and 43.65 ng/kg/min, respectively).

References *Last reviewed: February 19, 2015*

A Multicenter, Open-Label Study of the Safety and Tolerability of Transitioning From Remodulin® to Oral Treprostinil in Subjects with Pulmonary Arterial Hypertension. United Therapeutics. ClinicalTrials.gov Identifier: NCT01588405. http://clinicaltrials.gov/show/NCT01588405

Data on file. United Therapeutics Corporation. Research Triangle Park, NC 27709.

Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized controlled trial. *Circulation*. 2013 Feb 5;127(5):624-33. Epub 2013 Jan 10. http://www.ncbi.nlm.nih.gov/pubmed/23307827

Nathan SD, Feldman J, Hansdottir S, et al. Safety and feasibility of switching between oral and parenteral treprostinil. American Thoracic Society Meeting, Philadelphia, PA. May 17-22, 2013 (poster presentation).

Orenitram US Prescribing Information. United Therapeutics Corporation. Research Triangle Park, NC 27709.

Remodulin US Prescribing Information. United Therapeutics Corporation, Research Triangle Park, NC 27709.

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 Respir Crit Care Med. 2002 Mar 15;165(6):800-4 http://www.ncbi.nlm.nih.gov/pubmed/11897647

White RJ, Chakinala M, Rischard F, et al. Safety and tolerability of transitioning from parenteral treprostinil to oral treprostinil in patients with pulmonary arterial hypertension. American Thoracic Society Meeting, San Diego, CA. May 18-21, 2014 (verbal presentation).

White RJ, Jing ZC, Parikh K, et al. An open-label extension trial of oral treprostinil in subjects with pulmonary arterial hypertension. American Thoracic Society Meeting, Philadelphia, PA. May 17-22, 2013 (poster presentation).

TRANSITIONING PATIENTS FROM REMODULIN® (TREPROSTINIL) INJECTION TO ORENITRAM™ (TREPROSTINIL) EXTENDED-RELEASE TABLETS

INDICATIONS AND USAGE

Treprostinil injection is approved in the United States (US) under the name of Remodulin for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to diminish symptoms associated with exercise. [Remodulin USPI] Studies establishing effectiveness included patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). [Remodulin USPI; Simonneau, 2002] Treprostinil may be administered as a continuous subcutaneous (SC) infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous IV infusion should be reserved for patients who are intolerant of the SC route, or in whom these risks are considered warranted.

Oral treprostinil is approved in the US under the name of Orenitram for the treatment of PAH (WHO Group 1) to improve exercise capacity. [Orenitram USPI] The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). [Jing, 2013] When used as the sole vasodilator, the effect of oral treprostinil on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Oral treprostinil is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

TRANSITION FROM PARENTERAL TO ORAL TREPROSTINIL

United Therapeutics Corp. has completed a multicenter, open-label study of the safety, tolerability, and logistics of transitioning patients from SC/IV to oral treprostinil; however, only preliminary results are available [White, 2014; data on file]. As such, United Therapeutics Corp. cannot provide recommendations regarding this transition at this time. These preliminary data, as well as pharmacokinetic and dosing considerations, are discussed herein. We are aware of additional published reports of patients transitioned from SC/IV to oral treprostinil [Alvarez, 2012; Nathan, 2013; Coleman, 2015]; however, specific transition details and patient outcomes are not provided by the authors.

PHARMACOKINETIC AND DOSING CONSIDERATIONS

Treprostinil is a chemically stable prostacyclin analogue approved in the US for SC/IV (as Remodulin), inhaled (as Tyvaso®), and oral (as Orenitram) administration. In the plasma at physiological pH, both the treprostinil sodium (SC/IV and inhaled treprostinil formulations) and treprostinil diolamine (oral treprostinil) salts disassociate from their respective salt counterions and exist as the freely ionized form of treprostinil.

In the event of a planned, short-term treatment interruption in patients unable to take oral treprostinil, a temporary infusion of SC/IV treprostinil may be considered: “To calculate the total

daily dose (mg) of treprostinil for the parenteral route, divide the oral total daily dose by 5." [Orenitram USPI] Conversely, an equivalent total daily dose of oral treprostinil (in mg) can be estimated by multiplying the total daily dose of SC/IV treprostinil (in mg) by five. The following equation can be used to estimate an equivalent total daily dose of oral treprostinil in mg when a patient's dose of SC/IV treprostinil (in ng/kg/min) and weight (in kg) are available:

$$\text{Total daily oral treprostinil dose in mg} = \text{X ng/kg/min} \times 5 \times \frac{1\text{ mg}}{1{,}000{,}000\text{ ng}} \times \frac{1{,}440\text{ min}}{1\text{ day}} \times \text{patient's weight in kg}$$

- X ng/kg/min = dose of SC/IV treprostinil in ng/kg/min
- 5 = bioavailability factor based on the absolute bioavailability of oral treprostinil

Example estimation for a 70-kg patient receiving 25 ng/kg/min SC/IV treprostinil:

$$25\text{ ng/kg/min} \times 5 \times \frac{1\text{ mg}}{1{,}000{,}000\text{ ng}} \times \frac{1{,}440\text{ min}}{1\text{ day}} \times 70\text{ kg} = 12.6\text{ mg oral treprostinil daily}$$

A reference table for estimating equivalent total daily dose of oral treprostinil is provided at the conclusion of this letter (Table 4). Please note that this table is derived from the abovementioned equation and results in an estimation of a potential equivalent total daily dose of oral treprostinil (in mg), based on a patient's SC/IV treprostinil dose (in ng/kg/min) and weight (kg). This table does not provide precise equivalent total daily doses, and may result in an estimated equivalent total daily dose range. A patient's total daily dose of oral treprostinil may differ from estimations; oral treprostinil dosing is to be individualized according to clinical response. [Orenitram USPI]

The recommended starting dose of oral treprostinil is 0.25 mg twice daily (BID) with food, taken approximately 12 hours apart or 0.125 mg three times daily (TID) with food, taken approximately eight hours apart. [Orenitram USPI] Increase the dose as tolerated to achieve optimal clinical response. The recommended increment is 0.25 or 0.5 mg BID or 0.125 TID every three to four days. Upon repeat administration with a BID oral treprostinil regimen, accumulation of systemic exposures to treprostinil is minimal and results in a peak-to-trough ratio of approximately seven. A TID regimen will reduce the peak-to-trough fluctuations to approximately 2.5 for the same total daily dose.

OPEN-LABEL INVESTIGATION – PRELIMINARY RESULTS

A multicenter, open-label, 24-week study to investigate the safety, tolerability, and logistics of transitioning PAH patients from SC/IV to oral treprostinil was completed in 2014 (http://clinicaltrials.gov/show/NCT01588405). Final results from this study are expected in 2015. White et al. presented preliminary results from this study, including data from 33 enrolled patients. [White, 2014; data on file] Results should be interpreted with appropriate caution.

Patients were carefully selected and enrolled if they were clinically stable WHO functional class I or II, were stable (for at least 30 days) on SC/IV treprostinil (25-150 ng/kg/min) and one or

more PAH-specific oral therapies, had a baseline six-minute walk distance (6MWD) ≥ 250 meters, and had a cardiac index> 2.2 L/m/m^2, a peripheral vascular resistance < 10 Woods units, and a right arterial pressure < 11 mmHg (within 90 days of enrollment). Patients were hospitalized for the transition from SC/IV treprostinil to oral treprostinil to take place over approximately five days (if necessary for patient safety, the transition could be extended beyond five days). Initially, the study was designed to transition patients from SC/IV treprostinil to BID (every 12 ± 1 hours) oral treprostinil. Upon further investigation, a study amendment was implemented and all subsequently enrolled patients were transitioned to TID (every 8 ± 1 hours) dosing. Dosing was changed to more closely resemble the pharmacokinetics of SC/IV treprostinil (TID dosing reduces peak-to-trough fluctuations in plasma treprostinil concentration [Orenitram USPI]) and to potentially facilitate achievement of higher doses of oral treprostinil and reduce the occurrence of prostanoid-related adverse events, as compared with BID dosing. [data on file]

The dose of SC/IV treprostinil was decreased as the dose of oral treprostinil was increased during hospitalization. [data on file] Per study protocol, it was recommended to adjust the SC/IV treprostinil dose at approximately the same time oral treprostinil was given. If needed, SC/IV treprostinil dose could be adjusted more than three times daily. During the first 48 hours, oral treprostinil could not be increased more than 6 mg and SC/IV treprostinil could not be decreased more than 30 ng/kg/min within 24 hours. After 48 hours, both therapies were to be adjusted in accordance with investigator judgment.

Baseline demographics of the 33 patients enrolled are summarized in Table 1. All patients were transitioned from SC/IV treprostinil to oral treprostinil: 31 patients transitioned in ≤ five days and 2 patients required more than 5 days to transition. Seven patients (21%) were transitioned to BID oral treprostinil, three patients (9%) to BID then TID oral treprostinil, and 23 patients (70%) to TID oral treprostinil. Thirty-one patients completed the 24-week study and two patients discontinued from the study prematurely (discussed further herein).

Table 1. Baseline Demographics

Characteristic	n = 33
Age in Years: mean (range)	50 (18 - 80)
Gender: male : female	8 : 25
PAH Etiology: n (%)	
Idiopathic/heritable/appetite suppressant/stimulant use	23 (70)
Collagen vascular disease	7 (21)
Other (porto-pulm, HIV)	2 (6)
Congenital systemic-to-pulmonary shunt	1 (3)
Baseline 6MWD (meters): median (range)	446.5 (279-705)
Baseline Remodulin Dose (ng/kg/min): median (range)	57 (25 - 111)
Remodulin Route of Administration: (SC:IV)	28 : 5
Time on Remodulin (years): median (range)	3.5 (0.6-9.3)
PAH Background Therapy: n (%)	
ERA + PDE-5I	9 (27)
PDE-5I only	21 (64)
ERA only	3 (9)

6MWD: six-minute walk distance; ERA: endothelin receptor antagonist; HIV: Human Immunodeficiency Virus; IV: intravenous; PAH: pulmonary arterial hypertension; PDE-5 I: phosphodiesterase type 5 inhibitor; porto-pulm: portopulmonary; SC: subcutaneous
Source: data on file

Treprostinil doses and transition times are outlined by dosing regimen in Table 2. [data on file] Baseline SC/IV treprostinil doses ranged from 25.0 – 111.0 ng/kg/min. Total daily doses of oral treprostinil ranged from 9.0 – 60.0 mg after transition from SC/IV treprostinil (at the time SC/IV treprostinil dose was decreased to 0 ng/kg/min). Maximum total daily doses of oral treprostinil ranged from 10.5 – 82.5 mg (during the first 12 weeks of the study).

Table 2. Treprostinil Dose and Transition Time by Dosing Regimen

Dosing and Transition Time (First 24 Weeks of Study)	Dosing Regimen Mean ± SD Median (range)		
	BID (n=7)	BID + TID** (n=3)	TID (n=23)
Baseline Remodulin Dose (ng/kg/min)	51.1 ± 16.0 54.0 (25.0-73.0)	48.3 ± 8.5 45.0 (42.0-58.0)	62.7 ± 21.3 60.0 (27.0-111.0)
Remodulin to Oral Treprostinil Transition Time (days)	3.0 ± 0.0 3.0 (3.0-3.0)	10.7 ± 12.4 4.0 (3.0-25.0)	3.8 ± 1.1 4.0 (2.0-7.0)
Total Daily Dose of Oral Treprostinil (mg) After Transition*	18.4 ± 4.7 20.0 (10.0-25.0)	20.3 ± 1.5 20.0 (9.0-32.0)	33.8 ± 11.8 33.0 (11.0-60.0)
Maximum Total Daily Oral Treprostinil Dose (mg)***	23.6 ± 11.2 20.0 (10.5-45.5)	35.7 ± 14.8 35.5 (21.0 -50.5)	39.5 ± 14.4 38.8 (17.3-82.5)

BID: twice daily; SD: standard deviation; TID: three times daily
* Total daily dose of oral treprostinil at the same time parenteral treprostinil dose was decreased to zero (last day of transition)
** Subjects in this subgroup switched from BID to TID dosing at different time points in the 24-week study and all were on BID dosing at the time of transition from parenteral to oral treprostinil
*** Oral treprostinil doses were only recorded during the first 12 weeks of the study
Source: data on file

Median 6MWD achieved was 447 meters at Baseline (n=33) and 472, 464, and 467meters at Week 4 (n=32), Week 12 (n=29), and Week 24 (n=30), respectively. [data on file] Hemodynamics (assessed by echocardiography) at Baseline and Week 24 are summarized in Table 3. At Week 24, clinical measures of disease management appeared similar, with improvements in patient-reported treatment satisfaction and treatment convenience.

Table 3. Hemodynamics and Echocardiography

Assessment	Baseline mean ± SD (range)	Week 24 mean ± SD (range)	Mean Change from Baseline
PAPm (mmHg)	37.9 ± 12.7 (12 – 69)	40.0 ± 15.8 (13 – 73)	+2.2 ± 8.6 (-12 –26)
CO†* (L/min)	5.6 ± 1.5 (3 – 10)	5.3 ± 1.2 (3 - 8)	-0.3 ± 1.3 (-3 – 2)
CI†* ($L/min/m^2$)	3.0 ± 0.5 (2 – 4)	2.8 ± 0.6 (2 – 4)	-0.1 ± 0.7 (-1 – 1)
PCWP (mmHg)	10.1 ± 2.4 (5 – 14)	10.7 ± 3.5 (4 – 17)	+0.6 ± 4.6 (-8 - 11)
PVR† (mmHg*min/L)	5.2 ± 2.4 (1 - 9)	5.8 ± 3.5 (1 – 14)	+0.8 ± 2.4 (-3 - 8)
RAPm (mmHg)	5.9 ± 1.9 (2 – 8)	6.4 ± 2.9 (1 – 12)	+0.5 ± 3.7 (-7 – 8)
TAPSE‡ (cm)	2.0 ± 0.4 (1.1 – 3.0)	2.0 ± 0.4 (1.1 – 3.0)	+0.3 ± 0.3 (-0.6 – 0.6)

CI: cardiac index; CO: cardiac output; PAPm: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAPm: mean right artrial pressure; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion
n = 30, except where †n = 29 and ‡n = 33
*Both the thermodilution (n = 6) and Fick (n = 29) methods were used to determine CO; in cases where both methods were utilized, only the Fick method was used for CO and in the CI calculation
Source: data on file

Three times daily administration of oral treprostinil (~ every eight hours) resulted in sustained plasma concentrations throughout the dosing interval, similar exposure compared to parenteral treprostinil, and less difference between C_{max} and C_{min} levels compared to BID dosing (Figure 1). [data on file] Pharmacokinetic comparisons suggested that 0.84 mg TID oral treprostinil provides treprostinil exposure similar to 5 ng/kg/min SC/IV treprostinil for a 70-kg patient, but exposure variability is large amongst patients and influenced by predictable (e.g., Cytochrome P450 drug interactions) and unpredictable factors.

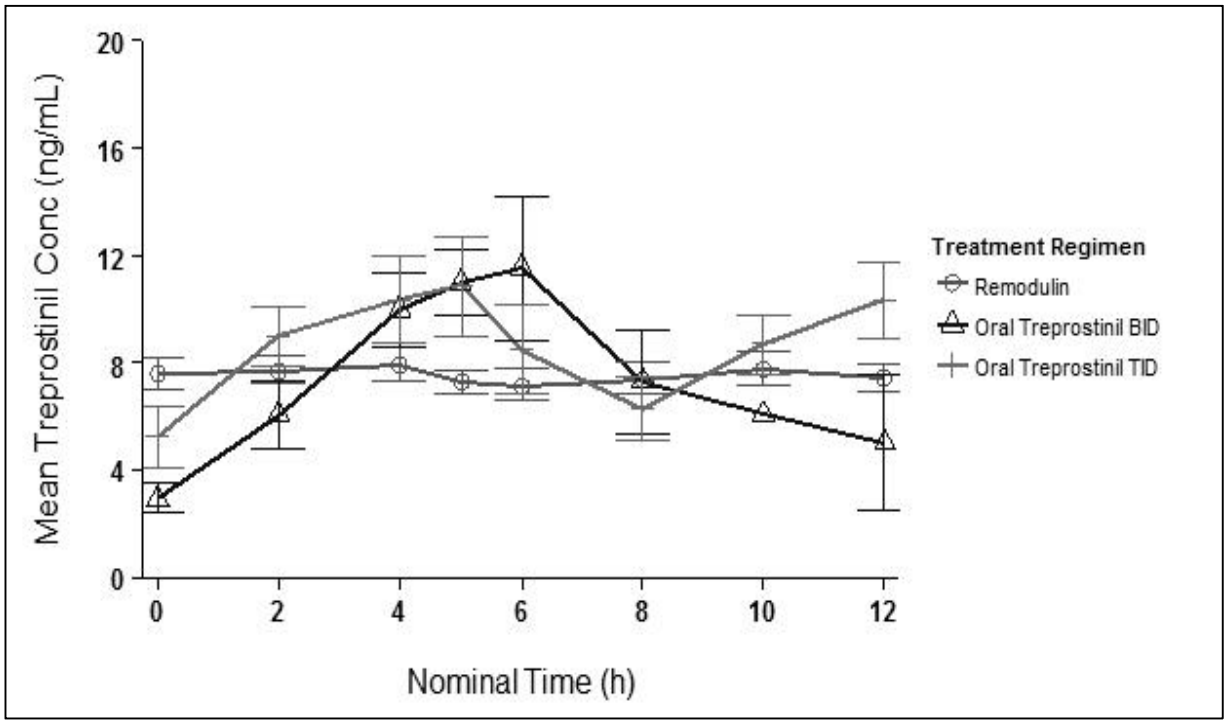

Figure 1. Mean ± Standard Error of the Mean Treprostinil Concentration vs. Time Plots by Treatment Regimen*

*Pharmacokinetic sampling was performed on two occasions during the study, at Baseline when patients were receiving SC/IV treprostinil (prior to commencing oral treprostinil) and at Week 24 when patients were receiving a stable dose of oral treprostinil.
BID: twice daily; TID: three times daily
Source: data on file

Adverse events reported by ≥ 30% of patients included: headache (85%), nausea (73%), flushing (70%), diarrhea (61%), fatigue (48%), vomiting (42%), dyspepsia (39%), dyspnea (39%), and upper respiratory tract infection (30%). Serious adverse events occurring in more than one patient included diarrhea (n = 2), nausea (n = 2), and vertigo (n = 2). Diarrhea and nausea were considered possibly related to oral treprostinil by the investigators. Two patients discontinued oral treprostinil due to serious adverse events. One patient had serious adverse events of abdominal distention, diarrhea, nausea, and acute renal failure. This patient's medical history included systemic sclerosis, CREST syndrome, chronic constipation, and bowel motility dysfunction. The patient received BID oral treprostinil for 25 days before discontinuing treatment secondary to abdominal distention, nausea, diarrhea, and CT-confirmed severe bowel wall edema. Over a 36-hour period, the patient transitioned back to previous parenteral treprostinil dose and adverse events resolved. The investigator assessed the events as possibly related to oral treprostinil and underlying disease, which lead to reduced absorption of oral treprostinil and subsequent hemodynamic decompensation. One patient had a serious adverse event of chronic hepatic failure, which was attributed to underlying concomitant illness by the investigator. No deaths occurred during the 24-week study period; however, the patient who discontinued oral treprostinil due to a serious adverse event of chronic hepatic failure died during the follow-up phase of chronic hepatic failure.

Patients transitioned in this study were carefully selected, clinically stable (WHO functional class I and II receiving other PAH therapies and having stable hemodynamics at baseline), and were receiving SC/IV treprostinil doses between 25.0 and 111.0 ng/kg/min prior to transition. Close follow-up is required post-transition to ensure that the dose of oral treprostinil is titrated to maintain the baseline PAH status achieved with SC/IV treprostinil.

Table 4. Reference Table for Estimating an Equivalent Total Daily Dose of Oral Treprostinil (mg) from Subcutaneous/Intravenous Treprostinil Dose (ng/kg/min) and Patient Weight (kg)

Patient Weight (kg)	Subcutaneous/Intravenous Treprostinil Dose (ng/kg/min)																Total Daily Oral Treprostinil Dose (mg)
	5	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	
40	1.44	2.88	4.32	5.76	7.20	8.64	10.08	11.52	12.96	14.40	15.84	17.28	18.72	20.16	21.60	23.04	
45	1.62	3.24	4.86	6.48	8.10	9.72	11.34	12.96	14.58	16.20	17.82	19.44	21.06	22.68	24.30	25.92	
50	1.80	3.60	5.40	7.20	9.00	10.80	12.60	14.40	16.20	18.00	19.80	21.60	23.40	25.20	27.00	28.80	
55	1.98	3.96	5.94	7.92	9.90	11.88	13.86	15.84	17.82	19.80	21.78	23.76	25.74	27.72	29.70	31.68	
60	2.16	4.32	6.48	8.64	10.80	12.96	15.12	17.28	19.44	21.60	23.76	25.92	28.08	30.24	32.40	34.56	
65	2.34	4.68	7.02	9.36	11.70	14.04	16.38	18.72	21.06	23.40	25.74	28.08	30.42	32.76	35.10	37.44	
70	2.52	5.04	7.56	10.08	12.60	15.12	17.64	20.16	22.68	25.20	27.72	30.24	32.76	35.28	37.80	40.32	
75	2.70	5.40	8.10	10.80	13.50	16.20	18.90	21.60	24.30	27.00	29.70	32.40	35.10	37.80	40.50	43.20	
80	2.88	5.76	8.64	11.52	14.40	17.28	20.16	23.04	25.92	28.80	31.68	34.56	37.44	40.32	43.20	46.08	
85	3.06	6.12	9.18	12.24	15.30	18.36	21.42	24.48	27.54	30.60	33.66	36.72	39.78	42.84	45.90	48.96	
90	3.24	6.48	9.72	12.96	16.20	19.44	22.68	25.92	29.16	32.40	35.64	38.88	42.12	45.36	48.60	51.84	
95	3.42	6.84	10.26	13.68	17.10	20.52	23.94	27.36	30.78	34.20	37.62	41.04	44.46	47.88	51.30	54.72	
100	3.60	7.20	10.80	14.40	18.00	21.60	25.20	28.80	32.40	36.00	39.60	43.20	46.80	50.40	54.00	57.60	

Example Estimation 1: Based on the above table, an estimated equivalent total daily dose of oral treprostinil for a 70-kg patient receiving 25 ng/kg/min SC/IV treprostinil is 12.6 mg oral treprostinil daily (row '70' x column '25' = 12.6 mg oral treprostinil daily).

Example Estimation 2: Based on the above table, an estimated equivalent total daily dose of oral treprostinil for a 83.25-kg patient receiving 30 ng/kg/min SC/IV treprostinil is between 17.28 – 18.36 mg oral treprostinil daily (rows '80' and '85' x column '30' = 17.28 and 18.36 mg oral treprostinil daily, respectively).

Example Estimation 3: Based on the above table, an estimated equivalent total daily dose of oral treprostinil for a 68-kg patient receiving 42.5 ng/kg/min SC/IV treprostinil is between 18.72 – 22.68 mg oral treprostinil daily (rows '65' and '70' x columns '40' and '45' = 18.72 and 20.16 and 21.06 and 22.68 mg oral treprostinil daily, respectively).

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