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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: Remodulin® (treprostinil) implantable system
Indication: For convenient delivery of treprostinil in the treatment of pulmonary arterial hypertension
Applicant: United Therapeutics Corp., Research Triangle Park, NC
Review Division: Cardiovascular and Renal Products
(DCRP/ODE1/OND/CDER)
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1 Executive Summary

1.1 Introduction

Treprostinil (Remodulin®) is a chemically stable prostacyclin (PGI₂) analog, with potent systemic and pulmonary vasodilating as well as antiplatelet effects, indicated for the treatment of pulmonary arterial hypertension (PAH). An injectable formulation of treprostinil has been approved for the treatment of PAH by continuous subcutaneous (sc) or intravenous (IV) routes. Infusion site pain and reactions, and catheter-related infection or sepsis were reported to be the most common adverse events among patients treated per sc or IV administration of treprostinil. The sponsor proposes that usage of a sterile implantable system may allow delivery of chronic infusion of treprostinil, as well as reduce adverse effects associated with the sc or IV routes. The proposed treprostinil implantable system design is based on the established drug delivery technology of the Implantable Intravascular Catheter (Model 10642), the SynchroMed® II Implantable Infusion System (Model 8637), and the N'Vision® Clinician Programmer (Model 8840) with SynchroMed II application software (Model 8870). The sponsor cross-referenced the studies conducted on treprostinil injection in the NDA 21-272 to support the supplemental NDA 208276.

1.2 Brief Discussion of Nonclinical Findings

In this supplemental NDA 505(b)(2), the deliverability of treprostinil was evaluated using the intravascular catheter (Model 10642) and the SynchroMed II infusion pump (Model 8637) implanted via the right jugular vein with final tip advanced into the superior vena cava slightly outside of the cardiac shadow in the dog. Animals were continuously infused at a rate of 22.5 µL/hr for 26 weeks, which corresponds to a treprostinil dosage of 12.5 ng/kg/min. The radiographs of the implanted system showed no evidence of dislocation, kinking or discontinuity, indicating stability and integrity of the implanted system. No occlusions of the catheters were observed as determined by the analysis of pump volumes, pressure waveforms, and radiographs. Gross and histopathological analysis revealed only mild local changes in the anterior vena cava associated with the physical presence of the indwelling implantable intravascular catheter. Tissue reactions to catheters containing treprostinil injection were similar to those containing saline. The plasma concentration of treprostinil achieved from the implantable system was comparable to that obtained by sc or IV routes of administration. The preclinical studies showed that the implantable pump and catheter system using Models 10642 and 8637 appear to deliver treprostinil in a continuous and consistent manner, and that catheter patency was maintained throughout the study duration with no significant adverse effects.

1.3 Recommendations

1.3.1 Approvability:

The extent and scope of the pharmacological and toxicological documentation provided are adequate to provide safety information on remodulin as delivered. The approvability of the Remodulin Implantable System will rely on the evaluations of the safety of the drug delivery device.

1.3.2 Labeling

The proposed prescribing information includes an appropriate description of the pharmacology, genotoxicity, carcinogenicity and reproductive and developmental toxicology.

2 Drug Information

2.1 Drug

Trade Name: Remodulin®

Generic Name: Treprostinil

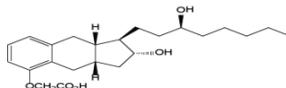
Chemical Name: Prostacyclin I₂ (PGI₂ analog)

Empirical formula: (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid

Molecular formula: C₂₃H₃₄O₅

Molecular Weight: 390.51

Structure:



Pharmacologic Class: Vasodilator

Route of administration: Implantable pump

2.2 Related INDs, NDAs

The NDA 21-272 supports the usage of treprostinil IV and sc at a starting infusion rate of 1.25 ng/kg/min, with increments of 2.5 ng/kg/min per week, for the treatment of PAH.

2.3 Drug Formulation

Treprostinil injection is a sterile solution of treprostinil formulated for sc or IV administration. Treprostinil will be supplied in 20 mL multi-dose vials in three strengths for the implantable system, containing 50 mg, 100 mg, or 200 mg (2.5 mg/mL, 5 mg/mL or 10 mg/mL) of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate (b) (4), and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Impurities from implants:

Characterization of leachable impurities from the implantable infusion system identified 30 organic chemicals and 8 inorganic chemicals per analysis of four leachate peaks (b) (4)

(b) (4) (ICH Q3C Impurities: Residual Solvents). The level of leachables for most chemicals was less than (b) (4) µg/day with the exception of (b) (4). The margins of safety (the ratio of Permitted Daily Exposure to the Daily Exposure/Daily Intake) of all leachables

exceed (b) (4), indicating that adverse effects are unlikely to occur from the chemicals leaching from the implantable system at the rates reported.

2.3 Clinical Indication and dosing regimen

Treprostinil implantable system is intended for the treatment of PAH by continuous IV infusion of treprostinil at mean Remodulin dosages of 72.2 ± 29.5 ng/kg/min (22 to 160 ng/kg/min) using the implantable intravascular catheter and infusion systems (Models 10642/8637). The remodulin implantable system delivers treprostinil at a concentration of 2.5, 5 or 10 mg/mL.

3 Studies Submitted

Studies Reviewed: The pharmacology, pharmacokinetics, toxicology, genotoxicity, carcinogenicity and reproductive toxicology of treprostinil are cross-referenced to the information in the original NDA 21-272. In addition, the study on treprostinil implantable catheter in the dog is reviewed.

4 Pharmacology

4.1 Primary Pharmacology

Treprostinil is a direct vasodilator of pulmonary and systemic arterial vascular beds, and an inhibitor of platelet aggregation.

4.2 Secondary Pharmacology

Secondary pharmacodynamics of treprostinil was not conducted.

Remodulin implantable system

Delivery of treprostinil with the implantable system serves an unmet medical need with a meaningful advantage over parenteral delivery using external pumps for drug delivery. The implantable system has the potential to address: i) patient convenience by reducing frequency of refills from every 2 - 3 days to 1 - 3 months; ii) compliance since there is no patient interaction required; iii) daily patient burdens because with an implanted system there is no drug admixture, catheter sets or infusion sets requiring patients to actively manage therapy on a daily basis; iv) catheter-related complications and infections because the implantable system is fully implanted; and overall quality of life issues since patients no longer have the restrictions associated with the external system.

Pharmacological activity of treprostinil

4.2.1. Platelet antiaggregatory activity

In vitro studies using human platelet-rich plasma showed that treprostinil caused a concentration-dependent inhibition of ADP-induced aggregation of human platelets, with an IC_{50} of 28.2 nM (11 ng/ml). Treprostinil was 20-fold less potent than prostacyclin in inhibiting the ADP-induced aggregation of human platelets.

4.2.2. Vascular relaxation effects

Treprostinil induced a concentration-dependent relaxation of isolated rabbit mesenteric artery segments precontracted with the thromboxane A₂ mimetic, U-46619. The order of potency when compared to other prostaglandins was treprostinil > carbacyclin (a stable PGI₂ analogue) > 16-dimethyl-PGE₂ > PGE₂. Treprostinil was 8 and 45 times more potent in inducing vascular relaxation than carbacyclin and PGE₂, respectively.

4.2.3. Antiproliferative effects

Treprostinil markedly reduced proliferation of cultured human pulmonary artery smooth muscle cells, as measured by cell counting (92% reduction) and [³H]-thymidine incorporation (61% reduction). In addition, treprostinil induced increase in intracellular cAMP to levels that were about 6-fold higher than control at 72 hours after drug treatment, indicating that treprostinil exerts persistent antiproliferative effect via a cAMP-dependent pathway in pulmonary artery smooth muscle cells.

4.2.5. Effects of Treprostinil on plasma angiotensin II concentrations

Treprostinil infusions dose-dependently increased plasma angiotensin II concentrations (50 - 263 pg/ml) that correlated inversely with reduced mean arterial blood pressure in anesthetized dogs. Prostacyclin (PGI₂), when given to anesthetized dogs for 4 hours at 0.01 to 0.3 µg/kg/min, produced vascular and cardiac effects similar to those produced by treprostinil; however, PGI₂ was 10 times more potent than treprostinil. PGI₂ infusions also dose-dependently increased plasma angiotensin II concentrations. Pretreatment with an angiotensin converting enzyme inhibitor, enalapril (0.3 mg/kg, iv), prevented the treprostinil-induced increases in plasma angiotensin II concentrations. Digoxin (100 mg/kg) pretreatment attenuated the ability of treprostinil to elevate plasma angiotensin II levels while pretreatment with a loop diuretic (furosemide, 1 mg/kg) potentiated the increase in plasma angiotensin II concentrations induced by treprostinil. These observations suggest that pretreatment with enalapril, digoxin or furosemide may enhance the cardiovascular effects of treprostinil.

4.3 Safety Pharmacology

4.3.1. Central nervous system:

In anesthetized cats, IV infusion of treprostinil, at 3 - 30 µg/kg/min for 20 minutes, had no effect on nictitating membrane contractions induced by cervical sympathetic nerve stimulation, or on bradycardia induced by vagal nerve stimulation, indicating that treprostinil had no effect on either the sympathetic or the parasympathetic components of the autonomic nervous system.

4.3.2. Respiratory system:

Treprostinil (10 - 100 nM) produced weak contractile responses in guinea pig isolated tracheal segments. In precontracted guinea pig tracheal preparations, treprostinil (10⁻⁸ - 10⁻³ M) caused concentration-related relaxation, with an ED₅₀ of 270 nM. Treprostinil was equipotent with PGE₂ (ED₅₀ = 220 nM) and about 400 times more potent than the stable prostacyclin analogue, carbacyclin (ED₅₀ = 100 µM). In anesthetized cats, IV infusion of treprostinil (3 - 30 µg/kg/min for 20 minutes) had minimal effects on both respiratory rate and

tidal volume except at the high dosage which increased respiratory rate by 10 - 15 breaths/min.

4.3.3. Cardiovascular (in anesthetized dogs):

Four hour IV infusions of treprostinil (0.1, 0.3, 1 and 3 µg/kg/min) in anesthetized dogs produced dose-dependent decreases in MAP (10 - 68%) and total peripheral resistance (TPR, 20 - 73%). Although decreases in pulmonary artery pressure and pulmonary vascular resistance (PVR, 9 - 33%) were observed, these effects were not dose-related. The vascular effects were rapid in onset, achieving maximum effect within 5 - 10 min of infusion with rapid recovery on termination of infusion. The effects on PVR were not dose-related, and plasma sample analysis showed a close relationship between plasma concentrations of treprostinil and changes in TPR and PVR. Pharmacodynamic modeling predicted maximum decreases in TPR of 66% and PVR of 22%. The plasma concentrations of treprostinil producing 50% of the maximum effect on systemic and pulmonary vascular resistances were 8.6 ng/ml and 11.3 ng/ml, respectively.

Treprostinil produced dose-dependent decreases in left ventricular inotropic (+dP/dt) activity at 1 and 3 µg/kg/min dosages, and significant dosage-dependent decreases in left ventricular lusitropic (-dP/dt) activity at dosages of 0.3 µg/kg/min and above. At 3 µg/kg/min, both +dP/dt and -dP/dt exhibited an apparent rebound above control values on termination of infusion. Significant decreases in left ventricular end diastolic pressure were noted at all dose levels. Cardiac output was significantly increased at 0.3 µg/kg/min and above and heart rate was increased at 0.3 and 3 µg/kg/min (30 - 68%). Treprostinil produced dose-dependent decreases in PR and QRS intervals with no significant effect on QTc.

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4.3.4. Cardiovascular (in conscious dogs):

(Study #: B071362, 12/2008)

In dogs, ten-minute IV infusions of treprostinil (0.3, 1 and 3 µg/kg/min) produced dose-related reductions of both systolic (18 - 40 mmHg) and diastolic (13 - 45 mmHg) blood pressures with increases in heart rates (13 - 30 bpm). These effects were rapid in onset and a full recovery was evident within 5 - 10 minutes of termination of infusion.

In conscious dogs, sc administration of treprostinil at dosages up to 0.03 mg/kg had no effect on blood pressure, heart rate, and electrocardiographic parameters, but at higher dosages ≥ 0.1 mg/kg significant decrease in systolic, diastolic, and mean blood pressure were observed at 0.5 hour, and significant increase in heart rate were observed at 1 and 2 hours after administration as compared to the vehicle control group (n=4 M/dose group). Treprostinil at 0.3 mg/kg had no effects on PR interval and QRS duration; however, significant decrease in systolic and diastolic blood pressure and mean blood pressure, and significant increase in heart rate, and significant prolongation in QTc values at 2 hours after administration were observed. These results indicate that treprostinil has effects on the blood pressure and heart rate at ≥ 0.1 mg/kg, and on QT interval at 0.3 mg/kg in conscious dogs. The high dosage of 0.3 mg/kg achieved a C_{max} 116.1 ng/ml, which is approximately 30-fold higher than the C_{max} of 3.6 ng/ml achieved in the clinical studies.

4.3.5. Gastrointestinal system:

Treprostinil exhibited weak contractile effects on isolated segments of guinea pig ileum, rat stomach or rat colon. When given orally, treprostinil inhibited GI motility and fluid secretion

in the rat small intestine. In rats, treprostinil inhibited ulcer formation induced by indomethacin or ethanol, suggesting that the anti-ulcer activity may be due to a cytoprotective rather than an antisecretory effect. In rats, pretreatment with a single dose of treprostinil (0.5 and 5 mg/kg, po) reduced the severity of carbon tetrachloride-induced hepatotoxicity. Treprostinil (0.03 - 10 mg/kg, po) had no effect on pentobarbital metabolism in rats, as measured by sleep duration, indicating absence of interaction with liver enzyme function.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Nonclinical pharmacokinetics of treprostinil is cross-referenced with the information in the NDA 21-272 and in peer-reviewed journals on treprostinil administered sc and IV.

5.1.1. Absorption

Treprostinil is relatively rapidly and completely absorbed after sc infusion, with an absolute bioavailability approximating 100% relative to intravenously administered treprostinil. Intravenously and subcutaneously administered treprostinil at a dosage of 10 ng/kg/min for 72 hrs achieved steady state plasma concentration of 1.09 ± 0.23 and 1.15 ± 0.19 ng/ml, respectively, and were considered to be bioequivalent.¹⁻³ The elimination half-life of treprostinil was 4.4 and 4.6 hours following IV and sc administration, respectively, which further demonstrates comparability of the two routes of administration at steady state.

5.1.2. Distribution

The volume of distribution of treprostinil in the central compartment is approximately 14L/70 kg ideal body weight. The pharmacokinetics of continuous sc administration of treprostinil were linear over the dose range of 1.25 to 125 ng/kg/min (corresponding to plasma concentrations of about 15 pg/mL to 18,250 pg/mL) and can be described by a two-compartment model. Treprostinil is 91% bound to human plasma protein.

5.1.2. Metabolism

Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% and representing 64.4% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuro-conjugated derivative (treprostinil glucuronide). The identified metabolites do not appear to have activity. Based on *in vitro* studies, treprostinil does not inhibit or induce major CYP enzymes.

5.1.3. Excretion

Administration of a single 8-hour sc infusion of [¹⁴C]-treprostinil (15 ng/kg/min), urinary excretion was the main route of elimination of [¹⁴C]-treprostinil-derived radioactivity (about 78% of the administered dose). Fecal elimination accounted only for about 12% of the administered dose.

5.2 Toxicokinetics

Toxicokinetics of treprostinil are cross-referenced to the information in the NDA 21-272.

6 General Toxicology

The general toxicology of treprostinil is cross-referenced to the previous studies in the NDA 21-272.

6.1 Single-Dose Toxicity of Treprostinil

In an acute dose study of treprostinil administered subcutaneously for 3 hrs in Sprague Dawley rats at dosages up to 500 ng/kg/min showed no adverse clinical signs.

6.2 Repeat-Dose Toxicity of Treprostinil

In a 14-day continuous sc infusion study at dosages ≥ 400 ng/kg/min in Beagle dogs, gross necropsy examination revealed intestinal intussusception and rectal prolapse. Histopathology findings consisted of moderate intussusception with hemorrhage, inflammatory cellular infiltrate, necrosis of the everted ileum and edema of rectum. The clinical signs observed in high dose animals included hypoactivity, emesis and loose stool. Edema with or without skin lesions at the injection sites was seen in treated and control dogs. There were no treatment-related hematology, clinical chemistry, EKG and organ weight findings in this study. The no-observed-adverse-effect-level (NOAEL) was considered to be 200 ng/kg/min.

In a 26-week sc continuous infusion toxicity study in rats at dosages up to 450 ng/kg/min, the most frequently observed clinical signs included the presence of lumps, swellings and/or thickening of the skin at or around the infusion site. The incidence and frequency of occurrence of infusion site findings were higher in all drug-treated groups compared to control groups, and also, the incidence of lesions at the site of infusion was greater in the high dosage animals than in lower dosage group animals. Dosage-related increased incidences of redness of the nose, pinnae, paws and/or tail were seen at 450 ng/kg/min (Css 20 ng/ml).

6.3 Treprostinil implantable catheter in dogs

Implanted catheter and pump drug delivery study

Study no.:	S1094
Study report location:	(b) (4)
Date of study completion:	September 23, 2005
GLP compliance:	Yes
Drug:	Treprostinil (1 mg/ml)
Formulation/Vehicle:	Saline (0.9% NaCL)
Route:	Venous catheter (Model 10642), connected to implanted drug pump (Model 8637, SynchroMed II, Medtronic)
Dosages:	540 μ L/day (0.0225 mL/hr) = 12.5 ng/min/kg
Species:	Canine
Weight:	25 – 30 kg
Number of rats:	N=12 (6/group), M/F

Study design: In a chronic 26-week study to evaluate the deliverability and safety of the venous catheter (Model 10642) connected to implanted drug pump (Model 8637 SynchroMed II), a total of twelve dogs were implanted via the right jugular vein with final tip advanced into the superior vena cava slightly outside of the cardiac shadow. At the time of implant, each pump was filled with 18 mL of infusate of either treprostinil (1 mg/mL) or saline. Animals were continuously infused via SynchroMed II infusion system programmed to deliver 540 μ L/day (3.8 mL/week) for 26 weeks, which computes to a treprostinil dosage of 15 or 12.5 ng/min/kg for a 25 kg and 30 kg dog, respectively. No anticoagulant was used.

Catheter stability: The radiographs of the implanted system showed no evidence of dislocation, kinking, or discontinuity thereby demonstrating stability and integrity of the implanted system. No occlusions of the catheters were observed in the study, as indicated by analysis of pump refill volumes, pressure waveforms, radiographs, and plasma treprostinil.

Accuracy of drug delivery: The average error over the study for each animal ranged from +7.3% (more volume delivered than programmed) to -1.2% (less volume delivered than programmed), which was well within the expected delivery accuracy specification of the SynchroMed II drug pump (\pm 14.5%).

Histopathology: Only mild local changes in the anterior vena cava associated with the physical presence of the indwelling implantable intravascular catheter were observed. Tissue reactions to catheters containing saline or treprostinil infusate were similar. Tissue morphological changes were similar to those previously reported in the implanted pacing leads in the right heart.

Plasma treprostinil: Mean plasma treprostinil concentrations of 1.03 ± 0.29 ng/mL were achieved, with an estimated plasma clearance of 364 mL/min (Figure 1, Panel A). The variances in treprostinil plasma levels were consistent and comparable between dogs over the 26-week study period (Figure 1, Panel B). Plasma treprostinil data reflect continuous and consistent delivery of treprostinil injection, which indicates that the catheters were patent throughout the study duration.

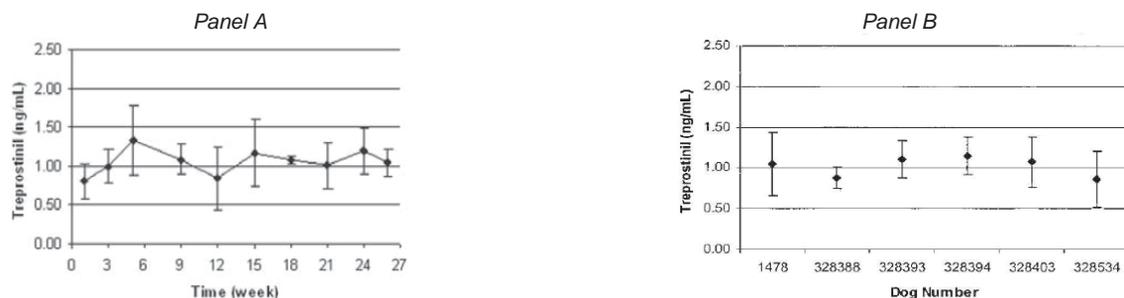


Figure 1. *Panel A:* Mean treprostinil plasma concentrations over 26 weeks (N=3-6).

Panel B: Variation in mean treprostinil plasma concentrations for each dog.

Summary: The implantable system showed continuous and consistent delivery of treprostinil with no significant adverse effects. The radiographs of the catheter body showed no evidence of kinking or a discontinuity indicating patency of the catheter body throughout the study duration. The plasma concentrations of treprostinil achieved from the implantable system were comparable to those achieved by sc or IV administration of treprostinil (⁴ Morris et al., 2008).

7 Genetic Toxicology

In vitro and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil.

7.1. *In vitro* mammalian cell mutation assay (in mouse lymphoma TK assay)

Study no.: 963729
Conducting laboratory: (b) (4) **Report date:** Jan 25, 2011
GLP compliance: Yes, **QA statement:** Yes
Drug: Treprostinil, **Batch #:** RD-UT-1066-082
Positive control: 4-Nitroquinoline-N-oxide (NQO), and Benzo(a)pyrene (BaP)
Negative control: Vehicle DMSO
Strains/cell line: Mouse lymphoma L5178Y cells TK^{+/-}

The ability of treprostinil to induce forward mutation in the mouse lymphoma L5178Y cells at the thymidine kinase locus was determined using concentrations of test article selected on the basis of viability of treated cells (Table 1). No substantial increases in mutation frequency were observed after treatment of cells with treprostinil at concentration levels up to the limit of toxicity in the presence and absence of metabolic activation (Table 1). It is concluded that treprostinil did not show any evidence of genotoxicity. In summary, treprostinil is not a mutagen in the mouse lymphoma cell assay.

Table 1: Percent increase in mutant frequency in mouse Lymphoma L5178 cell line

+ S9 mix (3 hr activation)			- S9 mix (24 hr activation)		
Treprostinil μ/mL	Cell growth (% viability)	Mutant Frequency	Treprostinil μg/mL	Cell growth (% viability)	Mutant Frequency
0	82	106	0	80	145
123	80	112	30.8	83	137
220	95	111	61.5	81	108
247	68	108	123	70	193
277	56	131	149	74	130
BaP (1 μg/mL)	66	447*	NQ (0.1 μg/mL)	56	464*

Positive control: NQO = 4-Nitroquinoline-N-oxide, BaP = Benzo(a)pyrene

8 Carcinogenicity

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil.

9 Reproductive and Developmental Toxicology

Treprostinil did not affect fertility or mating performance of male or female rats given continuous sc infusions at rates of up to 450 ng/kg/min [HED 73 ng/kg/min, about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials]. In pregnant rats, continuous sc infusions of treprostinil during organogenesis and late gestational development, at rates as high as 900 ng/kg/min (HED 146 ng/kg/min, about 117 times the starting human rate of infusion, and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous sc infusions of

treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng/kg/min (HED 49 ng/kg/min, about 41 times the starting human rate of infusion, and 5 times the average rate used in clinical trials). In rats, continuous sc infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng/kg/min, did not affect the growth and development of offspring.

10 Special Toxicology Studies

No special toxicology studies were performed.

11 Integrated Summary and Safety Evaluation

Treprostinil, a prostacyclin analogue is approved for delivery either subcutaneously or intravenously via an indwelling central venous catheter implant connected to an external (wearable) pump that stores and dispenses treprostinil. Subcutaneous delivery is associated with site pain and reactions which are sometimes intolerably severe. Studies have shown that the most common adverse effect of sc treprostinil is infusion site pain, which may lead to discontinuation of treatment. The proposed treprostinil implantable system is built upon the established drug delivery technology of the Medtronic SynchoMed II[®] platform (Models 8637, 10642) to provide a more convenient delivery of treprostinil in patients with pulmonary artery hypertension. In this supplemental NDA 208276, the sponsor is cross referencing the preclinical studies conducted for treprostinil (Remodulin[®]) injection under NDA 21-272. There are no changes to the treprostinil drug product other than labeling changes associated with the new implantable delivery system.

The deliverability of treprostinil from the implantable intravascular catheter was evaluated in chronic dog study implanted with a SynchroMed II infusion pump and an intravascular catheter via right jugular vein with final tip location in the superior vena cava just outside of the cardiac shadow. Animals were continuously infused at a rate of 540 μ L/day (0.0225 mL/hr), at a concentration affording a treprostinil dosage of 12.5 ng/kg/min for 26 weeks. The radiographs of the implanted system showed no evidence of dislocation, kinking, or discontinuity thereby demonstrating stability and integrity of the implanted system. No occlusions of the catheters were observed in the study per analyses of pump volumes, pressure waveforms, and radiographs. Gross and histopathological analysis revealed only mild local changes in the anterior vena cava associated with the physical presence of the indwelling implantable intravascular catheter. Tissue reactions to catheters containing saline or treprostinil injection were similar. The tissue changes were similar to those found with implanted pacing leads in other studies. The plasma concentrations of treprostinil achieved from the implantable system (1.03 ± 0.29 ng/mL) were comparable to those achieved by sc or IV administration of treprostinil. In summary, the implantable system (Models 10642 / 8637) delivered continuous and consistent delivery of treprostinil with no significant adverse effects, and the catheters were patent throughout the study duration.

Overall Conclusions

The preclinical studies showed that the implantable pump and catheter system using Models 10642 and 8637 appear to deliver treprostiniil in a continuous and consistent manner, and catheters remained patent throughout the study duration with no significant adverse effects.

Suggested labeling: Mutagenesis, Carcinogenesis, Impairment of fertility –

Mutagenesis: *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostiniil.

Carcinogenesis: Long-term studies have not been performed to evaluate the carcinogenic potential of treprostiniil.

Impairment of Fertility: Treprostiniil did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostiniil/kg/min [about 59 times the recommended starting human infusion at a rate of 1.25 ng/kg/min, and about 8 times the average infusion rate of 9.3 ng/kg/min achieved in clinical trials].

Pregnancy: In pregnant rats, continuous sc infusions of treprostiniil during organogenesis and late gestational development, at rates as high as 900 ng/kg/min (about 117 times the starting human rate of infusion, and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus.

In pregnant rabbits, effects of continuous sc infusions of treprostiniil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng/kg/min (about 41 times the starting human rate of infusion, and 5 times the average rate used in clinical trials).

In rats, continuous sc infusion of treprostiniil from implantation to the end of lactation, at rates of up to 450 ng/kg/min, did not affect the growth and development of offspring.

Because animal reproduction studies are not always predictive of human response, treprostiniil should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

12 Appendix/Attachments

References

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