CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 6-5-2017

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Renal Products

Drug: Implantable System for Remodulin (treprostinil); NDA 208276

Proposed Indications:
- Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise
- To diminish the rate of clinical deterioration in patients with pulmonary arterial hypertension requiring transition from Flolan® (epoprostenol sodium)

Proposed route of administration: Implantable system

Subject: Pregnancy and Lactation Labeling Rule (PLLR) conversion as part of NDA for new route of administration

Applicant: United Therapeutics

Materials Reviewed:
- Applicant's proposed labeling
- Approved Remodulin labeling (12-2014)
- Applicant's pregnancy and lactation safety review
- Literature review

Consult Question: Please assist with Pregnancy and Lactation Labeling

INTRODUCTION

The applicant submitted an NDA for a new delivery system for Remodulin (treprostinil) on December 15, 2016. Remodulin is currently approved as an injection for subcutaneous or intravenous use. The Division of Cardiovascular and Renal Products (DCRP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 5, 2017 to assist with Pregnancy and Lactation Labeling Rule (PLLR) labeling.

BACKGROUND

Product Background

Remodulin (treprostinil) is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness of Remodulin included patients with 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%) (1.1).

In patients with pulmonary arterial hypertension requiring transition from Flolan® (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.

Remodulin was approved in 2002 as an injection, for subcutaneous or intravenous use. Treprostinil is also marketed (by the same manufacturer) as an inhalation solution (Tyvaso) and an extended release tablet (Orenitram).

The half-life is 4 hours.

Reviewer comment

The receptor level mechanism of action is not described in approved labeling, but the literature describes different activity at different receptors. Unlike other prostacyclins that cause uterine contractions, treprostinil binds to the EP2 receptors that mediate vasodilation in the pulmonary vasculature, whereas uterine receptors are F2 and E2.[1]

Disease Background in Pregnancy

Data on pregnant women with PAH are limited. Pregnancies resulting in delivery occur rarely in women with PAH, as illustrated by results from a large US health survey reporting only 182 deliveries in patients with idiopathic PAH (IPAH) out of an estimated 11.2 million deliveries between 2002 and 2004.[2] A publication that summarized data from the Registry Of Pregnancy

[1] Mubarak KK. A review of prostaglandin analogs in the management of patients with pulmonary arterial hypertension. Respiratory Medicine 2010; 104; 9-21.

[2] Chakravarty EF *et al*. Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. Obstet Gynecol. 2008; 111(4): 927–9342008.

and Cardiac Disease (ROPAC) of the European Society of Cardiology, covering cases in Europe and Africa observed between 2008 and 2014, showed high maternal mortality (4/7) in patients with IPAH, while pregnancy outcomes in pulmonary hypertension due to left heart disease (most often affecting the mitral valve) appeared more favorable (3 maternal death cases in 112 pregnancies).[3] The 2015 *Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension* state that pregnancy is associated with a high risk of maternal and fetal mortality and that pregnancy should be discouraged.[2]

Current state of Remodulin labeling

Currently approved Remodulin labeling is in the Physician Labeling Rule format. Remodulin is labeled pregnancy category B, based on the lack of adverse developmental findings in animals at exposures 16 (rat) and 5 (rabbit) times the average rate used in clinical trials on a surface area basis. There is no information about human pregnancy in labeling.

The Nursing Mothers subsection states that it is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion.

Pregnancy and Lactation Labeling Rule (PLLR)

The Pregnancy and Lactation Labeling Rule (PLLR) went into effect on June 30, 2015.[4] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a new subsection, 8.3 Females and Males of Reproductive Potential, under Use in Specific Populations (8). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical Experience

No new nonclinical data were submitted with this NDA. The nonclinical PLLR revision is deferred to Dr. Belay Tesfamariam.

Applicant's Pregnancy Safety Review

1. Safety database

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[3] Sliwa K *et al*. ROPAC investigators. Pulmonary hypertension and pregnancy outcomes: data from the Registry of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. Eur J Heart Fail. 2016; 18(9):1119–28.

[4] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

In the period since initial marketing (May 21, 2002 to May 16, 2017), there were 137 reports of exposure during pregnancy with Remodulin, Tyvaso, and Orenitram with the following outcomes:

- normal newborn (n=42)
- delivery occurred; no additional information provided (n=31)
- unknown outcome (n=27)
- outcome pending (n=15)
- spontaneous abortion (n=7)
- elective abortion (n=11)
- maternal (and fetal) death (n=3)
- congenital malformations (n=1)
    - abnormalities of heart, lung, and kidney (not described)

The applicant concluded that these data do not indicate any new safety concerns.

Reviewer comment
Available case reports are not sufficient to inform the safety of treprostinil in pregnancy.

2. Literature Review

The applicant's review of the published literature resulted in identification of 14 case reports in which pregnant women were exposed to treprostinil predominantly in the second and third trimesters of pregnancy (see Appendix A). All 14 cases resulted in live births, with some preterm deliveries reported. One patient was exposed to treprostinil in the first trimester, however the publication does not report on whether any congenital malformations were present in the neonate.

Reviewer comment
DPMH performed a search of published literature on the safety of treprostinil in pregnancy and did not identify any additional publications.

Applicant's Pregnancy Conclusion

A review of all pregnancy cases did not reveal any patterns suggestive of a safety concern.

Reviewer comment
Available case reports are not sufficient to inform the safety of treprostinil in pregnancy.

Lactation

Nonclinical Experience

No new nonclinical data were submitted with this NDA.

Applicant's Lactation Safety Review

1. Safety database
   Two lactation cases were reported (no adverse reactions were reported).

2. Literature Review

There is a published report of a woman with PAH who was treated with intravenous treprostinil starting at 32 weeks gestation, and who breastfed for a year. The child was reported as being healthy at 2 years of age.[5]

Reviewer comment
DPMH performed a search of published literature on the safety of treprostinil in lactation and did not identify any additional publications. Medications and Mother's Milk concludes that treprostinil is probably compatible with breastfeeding and states the following: "Although there are no data at this time about the transfer of treprostinil into human milk, the oral bioavailability of this product is low; therefore, systemic concentrations in breastfed infants would most likely be low."[6] LactMed (the Drugs and Lactation Database) states the following: "If treprostinil is required by the mother, it is not a reason to discontinue breastfeeding. However, until more data are available, treprostinil should only be used with careful monitoring during breastfeeding".[7]

Applicant's Lactation Conclusion
The applicant concluded that limited available data not indicate any safety signals with the use of treprostinil during lactation.

Reviewer comment
DPMH concurs.

Infertility
Nonclinical Experience
No infertility effects were seen.

Applicant's Infertility Safety Review
No infertility cases were reported.

Reviewer comment
DPMH performed a search of published literature and no reports on infertility effects were found.

DISCUSSION

Pregnancy
There are only a limited number of published case reports of pregnancy exposure to treprostinil. The Risk Summary statement in Pregnancy labeling should reflect that there is insufficient data

[5] Franco V, Mueller J, Daniels CJ. Is the use of Remodulin safe for pregnant and breastfeeding patients with pulmonary arterial hypertension (PAH)? a case report. Heart Lung Transplant. 2012;31(Suppl. S):S71. [abstract]
[6] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.

[7] https://www.toxnet nlm nih.gov/cgi-bin/sis/search2/f?./temp/~1A6TnQ:3
The LactMed database is a National Library of Medicine database with information on drugs and lactation for healthcare practitioners and women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered.

to inform adverse developmental outcomes. PAH is associated with an increased risk of maternal and fetal mortality; it is appropriate to add this information under Clinical Considerations, Disease-associated maternal and embryo-fetal risk, per PLLR.

Lactation
There is only one published case report on treprostinil and lactation. This reported case did not identify adverse events; however this data is not sufficient to inform labeling. Inclusion of the risk-benefit statement, under PLLR, is appropriate for the Implantable System for Remodulin lactation labeling.

Females and Males of Reproductive Potential
Because there are no known infertility effects, this subsection is not needed.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with PLLR, as follows:

- 8.1 Pregnancy
  - The "Pregnancy" subsection of the Implantable System for Remodulin labeling was formatted in the PLLR format to include "Risk Summary", "Clinical Considerations", and "Data" sections.
- 8.2 Lactation
  - The "Lactation" subsection of the Implantable System for Remodulin labeling was formatted in the PLLR format to include the "Risk Summary" section.

DPMH LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of the proposed Implantable System for Remodulin labeling for compliance with PLLR. DPMH recommendations are below.
See final labeling for all of the labeling revisions negotiated with the applicant.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. However, there are risks to the mother and the fetus associated with pulmonary arterial hypertension *(see Clinical Considerations)*. In animal (b) (4) studies….. edits deferred to FDA Toxicology reviewers ….*(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality.

Data

Animal Data (edits deferred to FDA Toxicology reviewers)

In pregnant rats, continuous subcutaneous infusions of treprostinil during organogenesis and late gestational development, at doses as high as 900 ng treprostinil/kg/min (about 117 times the starting human (b) (4), on a ng/m2 basis and about 16 times the average (b) (4) achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous 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 a dose of 150 ng treprostinil/kg/min (about 41 times the starting human (b) (4), on a ng/m2 basis, and 5 times the average (b) (4) used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at doses of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. No treprostinil treatment-related effects on labor and delivery were seen in animal studies. Animal reproduction studies are not always predictive of human response.

8.2 Lactation

Risk Summary

There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production. (b) (4)

(b) (4)

APPENDIX A Published case reports of pregnant patients exposed to treprostinil (Applicant Table 1-2)

Publication	Patient	Pregnancy PAH Tx	Gestation Wk TRE Tx Initiated	Labor/Delivery PAH Tx	Delivery: Wk/ Fetal Outcome	Discharge PAH Tx
Franco 2012	35 yo CHD-aPAH	IV TRE	32	IV TRE: 26 ng/kg/min	Cesarean: 38/ Live birth	IV TRE: ~52 ng/kg/min
Smith 2012	35 yo PAH	IV TRE	32	IV TRE: 20 ng/kg/min	Cesarean: 37/ Live birth	IV TRE: 30 ng/kg/min
	37 yo IPAH	IV TRE	Throughout	IV TRE	Cesarean: 36/ Live birth	IV TRE: 142 ng/kg/min
	35 yo CHD-aPAH	IV TRE SIL: 20 mg TID	32	IV TRE: 20 ng/kg/min SIL: 20 mg TID	Vaginal: 37/ Live birth	IV TRE: 20 ng/kg/min SIL: 20 mg TID
	24 yo PAH with SLE	SIL	30	IV TRE: 12 ng/kg/min SIL	Vaginal: 30/ Live birth	IV TRE: 23 ng/kg/min SIL: 60 mg daily
Duarte 2013	25 yo CHD-aPAH	TRE	27	TRE: 22 ng/kg/min	Cesarean: 36/ Live birth	TRE, SIL
Preston 2014	Not provided	INH TRE and IV TRE	Not provided	IV TRE	Not provided/ Live birth	INH TRE
Sim 2014	27 yo CHD-aPAH	TRE	26	TRE: 10 ng/kg/min	Cesarean: 32/ Live birth	Not provided
Rosengarten 2015	30 yo CHD-aPAH	IV TRE	25	IV TRE: 25 ng/kg/min	Cesarean: 33/ Live birth	IV TRE Oxygen therapy
Kim 2015	26 yo CHD-aPAH	IV TRE SIL: 20 mg TID	~33	IV TRE: 25 ng/kg/min	Cesarean: ~33/ Live birth	SC TRE: 22 ng/kg/min Oxygen therapy
Liu 2016	5 x CHD-aPAH; 1 x CTD	Not provided	Not provided	IV and SC TRE: mean 18.5 ± 6.7 ng/kg/min	Cesarean x5: ~34/ Live birth Pregnancy termination x1	Not provided
Kaźnica-Wiatr 2016	25 yo CHD-aPAH	SIL	~33	TRE	Cesarean: ~33/ Live birth	BOS
	19 yo IPAH	TRE	22	TRE	Cesarean: 37/	TRE
		SIL		SIL	Live birth	
Leovic 2016	39 yo PH	SC TRE TAD	Not provided	IV TRE	Vaginal: ~34/ Unknown	Not provided

BOS, bosentan; CHD-aPAH, congenital heart disease associated pulmonary arterial hypertension; CTD, connective tissue disease; INH, inhaled; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; PH, pulmonary hypertension; TID, 3 times daily; TAD, tadalafil; TRE, treprostinil; Tx, therapy; SC, subcutaneous; SIL, sildenafil; SLE, systemic lupus erythematosus; Wk, week; yo, year old

Reference List of Published Case Reports Reported in Appendix A

Franco V, Mueller J, Daniels CJ. Is the use of Remodulin safe for pregnant and breastfeeding patients with pulmonary arterial hypertension (PAH)? a case report. Heart Lung Transplant. 2012;31(Suppl. S):S71. [abstract]

Smith JS, Mueller J, Daniels CJ. Pulmonary arterial hypertension in the setting of pregnancy: a case series and standard treatment approach. Lung. 2012;190(2):155-160.

Preston IR, Feldman J, White J, et al. Safety and efficacy of transition from inhaled treprostinil to parenteral treprostinil in selected patients with pulmonary arterial hypertension. Pulm Circ. 2014;4(3):456-461.

Sim H, Lee MJ, Lee JH, et al. Successful management in a pregnant woman with Eisenmenger's syndrome undergoing emergency cesarean section under general anesthesia. Korean J Anesthesiol. 2014:67(Suppl):S69-S71.

Rosengarten D, Kramer R. Pregnancy in a woman with pulmonary hypertension: favorable outcome with intravenous treprostinil. Clin Exp Obstet Gynecol. 2015;42(3):390-391.

Kim GS, Yang M, Chang CH, et al. Management of cardiac arrest in a parturient with Eisenmenger's syndrome and complete atrioventricular block during Cesarean section: a case report. Korean J Anesthesiol. 2015;68 (6):617-621.

Liu B, Huang X, Zhang W, et al. Use of treprostinil in pregnant women with pulmonary arterial hypertension during peripartum period. Am J Respir Crit Care Med. 2016;193:A7374. [abstract]

Kaźnica-Wiatr M, Leśniak-Sobelga A, Kopeć G, et al. Pregnancy in pulmonary arterial hypertension. J Rare CV Dis. 2016;2 (7):215-219.

Leovic MP, Robbins HN, Foley MR, et al. The "virtual" obstetrical intensive care unit: providing critical care for contemporary obstetrics in nontraditional locations. Am J Obstet Gynecol. 2016;215(6):736-738.

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/s/

LEYLA SAHIN
06/05/2017

TAMARA N JOHNSON
06/05/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 26, 2016

To: Wayne Amchin, RAC, MPA
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

From: Puja Shah, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208276
Remodulin Implantable System/Remodulin (treprostinil) injection

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OPDP acknowledges the receipt of your February 18, 2015, labeling consult request regarding the proposed Package Insert (PI), Carton/Container Labeling (CCL), and Instructions for Use (IFU) for Remodulin Implantable System/Remodulin (treprostinil) injection. Reference is made to the complete response (CR) letter issued by DCaRP to the Applicant on October 8, 2016. In the CR letter, DCaRP notes that on March 11, 2016, FDA issued a Not Approvable letter on the device component in this drug-device combination product, which was submitted under a Premarket Approval Application. Additionally, DCaRP notes that there are insufficient data to evaluate the risk of potential patient exposure to microbial contaminants. As such, a substantially complete PI was not sent to OPDP for review. Therefore, OPDP defers comment on the Applicant's PI, CCL, and IFU at this time.

OPDP requests that DCaRP submit a new labeling consult request during the subsequent review cycle.

If you have any questions, please contact Puja Shah 240-402-5040. Thank you.

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/s/

PUJA J SHAH
10/26/2016