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APPLICATION NUMBER:

208276Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 6-5-2017

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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

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