CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214522Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 9, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214522
Product Name and Strength:	Tadliq (tadalafil) oral suspension, 20 mg/5 mL
Applicant/Sponsor Name:	CMP Development LLC
OSE RCM #:	2020-895-2
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label received on May 13, 2022 for Tadliq. We reviewed the revised container label for Tadliq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Mehta, H. Label and Labeling Review for Tadliq (NDA 214522). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 14. RCM No.: 2020-895-1.

Reference ID: 4996847

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HINA S MEHTA
06/09/2022 02:27:09 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 14, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214522
Product Name, Dosage Form, and Strength:	Tadliq (tadalafil) oral suspension, 20 mg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CMP Development LLC
FDA Received Date:	February 10, 2021 and December 21, 2021
OSE RCM #:	2020-895-1
DMEPA Team Leader:	Hina Mehta, PharmD

Reference ID: 4968865

1 REASON FOR REVIEW

As part of the approval process of the 505(b)(2) NDA class 2 resubmission for Tadliq (tadalafil) oral suspension we reviewed the proposed container label, Prescribing Information (PI), and Patient Information for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

CMP Development LLC, submitted Tadliq (tadalafil) oral suspension (NDA 214522) on April 23, 2020, a 505(b)(2) application which relies upon the listed drug Adcirca (tadalafil) tablets under NDA 022332. Adcirca (tadalafil) tablet is currently approved as 20 mg tablets. The proposed product will be available as a 20 mg/5 mL oral suspension.

The application received a complete response (CR) on February 23, 2021 for facility deficiencies. We previously reviewed the label and labeling.[a] However, comment on the proposed labeling were reserved until the application is otherwise adequate. CMP Development LLC. Submitted a response to the CR letter on December 21, 2021. We note CMP Development LLC did not resubmit the labels and labeling with the CR response however, they referenced the labeling submitted on February 10, 2021.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

CMP Development LLC resubmitted a 505(b)(2) NDA to obtain marketing approval for Tadliq (tadalafil) oral suspension. The Listed Drug (LD) for this product is Adcirca (tadalafil) tablet. We note that the proposed Tadliq (tadalafil) oral suspension has the indication and same dosage

[a] Straka, M. Label and Labeling Review for Tadliq (NDA 214522). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 24. RCM No.: 2020-895.

Reference ID: 4968865

regimen (40 mg once daily. However, there are differences in the proposed dosage form as Tadliq will be available as a 20 mg/5 mL oral suspension; unlike the listed drug Adcirca which is available as 20 mg tablets.

We performed a risk assessment of the proposed container label, PI, and patient information for Tadliq (tadalafil) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI and patient information did not identify any areas of concern from a medication error perspective. We identified areas on the container label that can be modified to improve the clarity of the information presented. We note that there is a graphic design present on the container label that appears to be part of the proprietary name and competes in prominence with the proprietary name that may contribute to medication errors. We provide recommendations for CMP Development in Section 4.1 below.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for CMP Development LLC. in Section 4.1 below.

4.1 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. As currently presented the graphic competes in prominence with the proprietary name and other important information on the principal display panel (PDP) such as the strength and proprietary name. It may also be misinterpreted as part of the proprietary name. Ensure that the graphic does not compete in prominence with the pertinent information on the PDP.
2. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tadliq received on February 10, 2021 from CMP Development LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Tadliq and the Listed Drug

Product Name	**Tadliq**	**Adcirca**[b]
Initial Approval Date	N/A	May 22, 2009
Active Ingredient	tadalafil)	tadalafil
Indication	Tadliq is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.	ADCIRCA is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.
Route of Administration	oral	oral
Dosage Form	oral suspension	tablet
Strength	20 mg/5 mL	20 mg
Dose and Frequency	40 mg (10 mL) once daily	40 mg once daily
How Supplied	TADLIQ (tadalafil) Oral Suspension, 40 mg/10 mL is a white to off-white, opaque, peppermint-flavored suspension. It is available in a 150 mL bottle (NDC 46287-045-15)	ADCIRCA (tadalafil) is supplied as follows: 20 mg orange, film–coated, almond–shaped tablets (not scored), debossed with "4467" Bottles of 60 NDC 66302-467-60
Storage	Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Shake well before use.	Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep out of reach of children.
Container Closure	Tadalafil Oral Suspension, 4 mg/mL is packaged in 150 mL (b) (4) bottle (b) (4)	HDPE bottle with a silica gel dessicant.

[b] Adcirca [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2017 May 5. Available from: https://www.accessdata fda.gov/drugsatfda_docs/label/2017/022332s009lbl.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Tadliq labels and labeling submitted by CMP Development LLC.

- Container label received on February 10, 2021
- Prescribing Information (Image not shown) received on February 10, 2021, available from \\CDSESUB1\evsprod\nda214522\0009\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi-track.pdf

G.2 Label and Labeling Images

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HINA S MEHTA
04/14/2022 01:33:22 PM

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

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

Memorandum

Date: January 4, 2021

To: Christine Sadr, Regulatory Health Project Manager
Cardiology and Nephrology / Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: Zarna Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TADLIQ® (tadalafil oral suspension)

NDA/BLA: 214522

In response to DCN consult request dated May 14, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and the carton and container labeling for TADLIQ® (tadalafil for oral suspension).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN (Christine Sadr) on December 18, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on December 31, 2020.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the sponsor to the electronic document room on April 23, 2020, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

25 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ZARNA PATEL
01/04/2021 03:07:07 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 30, 2020
To:	Christine Sadr, MS Regulatory Project Manager **Division of Cardiovascular and Renal Products (DCaRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name)/Dosage Form and Route:	TADLIQ (tadalafil oral suspension)
Application Type/Number:	NDA 214522
Applicant:	CMP Development LLC

1 INTRODUCTION

On April 23, 2020, CMP Development LLC submitted for the Agency's review an original New Drug Application (NDA) 214522 for TADLIQ (tadalafil oral suspension). The proposed indication for TADLIQ (tadalafil oral suspension) is the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCaRP) on June 26, 2020, and May 14, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TADLIQ (tadalafil oral suspension).

2 MATERIAL REVIEWED

- Draft TADLIQ (tadalafil oral suspension) PPI received on April 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 18, 2020.
- Draft TADLIQ (tadalafil oral suspension) Prescribing Information (PI) received on April 23, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 18, 2020.
- Approved Referenced Listed Drug labeling for ADCIRCA (tadalafil) NDA 022332 dated September 15, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

5 Pages of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA M CHUNG
12/30/2020 03:50:30 PM

ZARNA PATEL
12/30/2020 03:52:56 PM

BARBARA A FULLER
12/31/2020 07:28:16 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 10/16/2020 **Date consulted:** 7/19/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Cardiovascular and Nephrology (DCN)

Drug: Tadliq (tadalafil) Oral Suspension, 4mg/ml

NDA: 214522

Applicant: CMP Development, LLC

Subject: new NDA

Proposed Indication: Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214522
- DCN consult form for DPMH, DARRTS Reference ID 4648694

Reference ID: 4686961

- DPMH review of ADCIRCA (tadalafil), NDA 22332, by Catherine Roca, MD, on May 31, 2019, DARRTS Reference ID 4441500[1]
- DPMH review of Revatio (sildenafil) NDA 21845 by Catherine Roca, MD, on September 22, 2017. DARRTS Reference ID 4157089[2]
- DPMH review of Revatio (sildenafil) NDAs 21845, 203109, 22473 by Wenjie Sun, MD on October 15, 2020. DARRTS Reference ID 4680974[2]

Consult Question:

- DCN is seeking assistance from DPMH in developing Sections 8.1, 8.2 and 8.3 of the product's labeling.

INTRODUCTION AND BACKGROUND

On April 23, 2020, the applicant (CMP Development, LLC) submitted a new NDA 214522 for Tadliq (tadalafil) Oral Suspension for approval. The Division of Cardiovascular and Nephrology (DCN) consulted the Division of Pediatric and Maternal Health (DPMH) on July 29, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Tadalafil was first approved on November 21, 2003, in the United States in a tablet formulation as Cialis, indicated for the treatment of erectile dysfunction. Tadalafil was first approved on May 22, 2009, for the indication for the treatment of pulmonary arterial hypertension (PAH) (WHO Group1) to improve exercise ability.
- On April 23, 2020, the applicant (CMP Development, LLC) submitted a new NDA 214522 for Tadalafil Oral Suspension 4mg/ml, a new formulation, with the proposed indication for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.
- This approval is based on the 505(b)(2) regulatory pathway of the Federal Food, Drug, and Cosmetic, which relies on the Agency's previous finding of safety and effectiveness of the reference listed drug (RLD), ADCIRCA (Tadalafil) tablets, 20mg (NDA 022332), approved May 22, 2009.

Drug Characteristics and Labeling

Drug Class	phosphodiesterase 5 (PDE5) inhibitor
Mechanism of action	Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP

[1] The Adcirca review was part of the materials reviewed to avoid duplicating background information and literature relevant to the underlying medical condition but was not a source relied upon for the labeling recommendations below.

[2] The Revatio review was part of the materials reviewed to avoid duplicating background information and literature relevant to the underlying medical condition but was not a source relied upon for the labeling recommendations below.

	resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.
Molecular weight	389.41 g/mol
Half-life	15 hours
Protein Binding	94%
Bioavailability	not determined
Metabolism	Tadalafil is predominantly metabolized by CYP3A to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide. Tadalafil is excreted predominantly as metabolites, mainly in the feces (approximately 61% of the dose) and to a lesser extent in the urine (approximately 36% of the dose).
Serious Adverse Reactions	Hypotension, visual loss, hearing loss and priapism

Current State of the Labeling for the approved RLD, ADCIRCA tablets

- Approved labeling is in the Physician Labeling Rule (PLR) format and the PLLR format.
- There is no boxed warning for this drug.
- There are contraindications for use of ADCIRCA
    - Concomitant organic nitrate
    - Concomitant Guanylate Cyclase (GC) Stimulators
    - History of known serious hypersensitivity reaction to ADCIRCA or CIALIS

(b) (4)

[redacted]

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

REVIEW

PREGNANCY

Condition: Pulmonary arterial hypertension and pregnancy[3,4,5,6]

- The prevalence of PAH varies from 11-26 per million adults; it is 4 times more common in women than men.[7]
- Pregnancy in patients with pulmonary hypertension is associated with an increased risk of maternal and fetal death. The introduction of pulmonary vasodilator therapy has resulted in a significant decline in maternal mortality rates, which is uniform across all prominent PH registries with a reduction from 30-17% in idiopathic PAH, 36-28% in Eisenmenger's syndrome, and 56-33% in PAH of other causes.[5]
- PAH in pregnancy can increase the risk of worsening pulmonary vascular hemodynamics, precipitate acute cardiovascular collapse in the mother and death, and result in placental hypoperfusion and fetal hypoxemia. Many women with PAH choose to avoid pregnancy. In general, estrogen-containing contraceptives should be avoided since estrogen is thought to play a role in the pathogenesis of PAH.[6]
- It is unknown whether the risk of fetal abortion is increased but fetal hypoxemia may be an issue in those with maternal hypoxemia from PAH. There are some data that fetal demise is increased.[8,9] Also, chronic maternal hypoxemia would be expected to increase the risk for fetal growth restriction.
- Patients with PAH usually deteriorate in the second trimester of pregnancy. The causes of poor maternal outcomes are varied and include risk of death from right heart failure and stroke from intracardiac shunting.[10]
- There is a high peri-/post-partum risk due to hemodynamic stress, bleeding complications and the use of general anesthesia, which can all lead to right heart failure.[4,11] The first 24 to 36 hours after delivery is the time of greatest risk and death.[5] The majority of maternal deaths occurred within a month after delivery.[6]

[3] DPMH review of Revatio (sildenafil) NDA 21845 by Catherine Roca, MD, on September 22, 2017. DARRTS Reference ID 4157089

[4] DPMH review of ADCIRCA (tadalafil), NDA 22332, by Catherine Roca, MD, on May 31, 2019, DARRTS Reference ID 4441500

[5] Hopkins W, et al. Treatment and prognosis of pulmonary arterial hypertension in adults (group1). UpToDate. Accessed 8/14/2020.

[6] Aryal SR, et al. Managment of reproductive health in pateints with pulmonary hypertension. AJOG MFM May 2020

[7] Thenappaan T, et al. Pulmonary arterial hypertension: pathogenesis and clinical management. BMJ. 2018; 14:360.

[8] Sun X, Feng J, Shi J. Pregnancy and pulmonary hypertension: An exploratory analysis of risk factors and outcomes. Medicine (Baltimore) 2018; 97:e13035.

[9] Thomas E, Yang J, Xu J, et al. Pulmonary Hypertension and Pregnancy Outcomes: Insights From the National Inpatient Sample. J Am Heart Assoc 2017; 6.

[10] Hsu CH, et al. The management of pregnancy and pregnancy-related medical conditions in pulmonary arterial hypertension patients. Int J Clin Pract Suppl 2011; 175: 6–14.

[11] Jais X, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 2012; 40: 881–885.

- The most common risk to the fetus is death.[12] There are high rates of preterm deliveries ranging from 85 to 100% and fetal growth restriction in up to one-third of pregnancies.[13]

Nonclinical Experience

In animal reproduction studies, no adverse developmental effects were observed with oral administration of tadalafil to pregnant rats or mice during organogenesis at exposures 7 times the exposure at the maximum recommended human dose (MRHD) of 40 mg/day based on AUC.

The reader is referred to the full Pharmacology/Toxicology review by John Koerner, Ph.D. on March 6, 2009.

Review of Clinical Trials

Since the application was submitted under the 505(b)(2) pathway, the applicant is relying on the Agency's findings of safety and effectiveness for NDA 022332. The applicant submitted an oral bioequivalence study. No pregnant women were enrolled.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published literature including Pubmed, LactMed[14] and PubChem[15] regarding tadalafil use in pregnancy. The applicant found four relevant publications regarding the use of tadalafil in pregnancy, which are listed below. For a full account of the applicant's review of literature in pregnancy, refer to the applicant's July 27, 2020 submission, Module 1.14.1.3, under "Review of Pregnancy, Lactation, and Reproductive Potential" (sequence number 003).

- In a small clinical trial, 12 pregnant women between 22-33 weeks' gestation with diagnosis of intrauterine growth restriction (IUGR) (estimated fetal weight (EFW) < 10%) were administered oral tadalafil at doses of 10, 20, or 40 mg/day (3, 3, and 6 cases, respectively) until delivery or 37^{+6} weeks' gestation. Maternal adverse events of at least grade 1 (headache, breast discomfort, palpitation, facial flushing, nasal hemorrhage) were recorded in all treatment groups. However, these adverse events were all determined to be acceptable from the viewpoints of the mothers. No major adverse events were seen in the 10 and 20 mg/day treatment groups. One patient in the 40 mg/day group experienced intrauterine fetal distress leading to fetal death. However, the safety evaluation committee determined this event to be a result of velamentous insertion of the umbilical cord, unrelated to tadalafil. Based on these results, the authors concluded that tadalafil has a favorable safety profile for pregnant women and fetuses with IUGR.[16]

[12] Gleicher N, et al. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv 1979; 34: 721–741.

[13] 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.

[14] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility.

[15] https://pubchem.ncbi.nlm.nih.gov/compound/110635

[16] Kubo M, Tanaka H, Maki S, et al. Safety and dose-finding trial of tadalafil administered for fetal growth restriction: A phase-1 clinical study. The Journal of Obstetrics and Gynaecology Research. 2017;43(7):1159-1168.

Reviewer Comment: This was a dose-escalating trial. Safety was assessed but effects of tadalafil on IUGR were not assessed.

- In a retrospective study, 11 pregnant women with IUGR receiving tadalafil along with the conventional management for IUGR were matched with 14 pregnant women with IUGR receiving conventional management alone (the authors specified that conventional management for IUGR followed guidelines for management of IUGR based on obstetrical practice in Japan in 2014 including fetal nonstress test, prenatal ultrasounds and antenatal steroids). Maternal and perinatal outcomes were assessed, and the authors found that both birthweight and fetal growth velocity from enrollment to birth were higher in the tadalafil group than in the conventional management group. The number of cesarean deliveries were approximately two-fold higher in the conventional management group than the tadalafil group. Importantly, cesarean section due to non-reassuring fetal status was performed in seven pregnant women in the conventional management group (58.3%) but in none in the tadalafil group ($P < 0.05$, chi-squared test). The authors concluded tadalafil may improve perinatal outcome in IUGR by modulating fetal growth.[17]

- Furuhashi et al.[18] conducted a safety trial of tadalafil in 8 pregnant women at 26-37 weeks gestation with preeclampsia. There were no maternal adverse events at the lowest dose (10 mg/day) of tadalafil. At 20 and 40 mg/day, grade 1 headache and palpitation were recorded, but all resolved spontaneously. There were no fetal adverse events, and all observed neonatal adverse events were thought to be caused by prematurity and not related to tadalafil (Grade 1 vomiting, meconium plug syndrome, 2 cases of jaundice, 2 cases of respiratory distress syndrome). The authors concluded tadalafil as treatment for preeclampsia was deemed to be tolerable and safe for the mother and fetus at all tested doses.

- A prospective study of nine pregnant women without cardiovascular disease who were using tadalafil to treat fetal growth restriction, the authors concluded that tadalafil did not adversely affect pregnant women without cardiovascular disease. Fetal outcomes were not reported.[19]

The applicant concluded:

"Human and animal studies show no evidence of maternal or fetal harm as a result of tadalafil dosing. The Tadliq package insert (b) (4) [redacted]. However, as available clinical data on administration of tadalafil in pregnant women remains limited to a few studies, the Tadliq package insert (b) (4) [redacted]

[17] Kubo M, Umekawa T, Maekawa Y, et al. Retrospective study of tadalafil for fetal growth restriction: Impact on maternal and perinatal outcomes. The Journal of Obstetrics and Gynaecology Research. 2017;43(2):291-297.
[18] Furuhashi FH, Tanaka H, Kaneda MK, et al. Safety trial of tadalafil administered for the treatment of preeclampsia. The Journal of Maternal-Fetal & Neonatal Medicine. 2020;33(1):167-170.
[19] Tanaka K, et al. Cardiac function and tadalafil used for treating fetal growth restriction in pregnant women without cardiovascular disease. Journal of Maternal-Fetal and Neonatal Medicine 2019; 32(15): 2460-2462.

Reference ID: 4686961

Reviewer comment:
There are limited number of studies evaluating of tadalafil use in pregnancy identified in the literature. Almost all studies are limited to tadalafil use in the second and third trimester of pregnancy and used for the treatment of preeclampsia or IUGR in pregnancy. Therefore, the effects of tadalafil on miscarriages or fetal malformations cannot be assessed.

DPMH's Review of Literature
In the 2019 DPMH review of tadalafil by Catherine Roca, MD,[4] DPMH noted:

> "Data from the published literature and the applicant's pharmacovigilance database do not indicate a clear risk of adverse pregnancy outcomes."

See APPENDIX A for a summary of previous DPMH reviewed literature of the use of tadalafil in pregnancy.

DPMH conducted an updated published literature review, since 2019, using Embase, Pubmed, Micromedex,[20] ReproTox,[21] TERIS,[22] and Shepard's.[23] Search terms used were "tadalafil" AND "pregnancy," "tadalafil" AND "pregnancy" AND "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage." Three new relevant publications were found.

- In a prospective randomized phase II trial conducted in Japan (Maki et al), 89 pregnant women with fetal growth restriction were treated with tadalafil 20 mg/day versus conventional treatment starting at the 2nd and 3rd trimester of pregnancy through delivery. The Maki et al study was stopped early due to lack of efficacy and possible safety findings reported in another study- the Dutch arm of the Sildenafil TheRapy in Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER)[24] trial. Although an initial report published in 2019, by Maki et al,[25] precluded fetal outcomes, in an updated publication, the authors reported there were 7 deaths (4 fetal, 1 neonatal, and 2 infants) in the control group and 1 neonatal death in the tadalafil group. Maki et al. concluded that there were decreased fetal and infant deaths associated with fetal growth restriction, which they thought was due to prolongation of pregnancy. [26]
  Reviewer comment: The Maki et al study was originally supposed to enroll 140 fetuses with fetal growth restriction but only ended up enrolling 89 patients. The authors

[20] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 8/7/2020.
[21] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/7/2020.
[22] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 8/7/2020.
[23] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 8/7/2020.
[24] Pels A, et al. Maternal Sildenafil vs Placebo in Pregnant Women with Severe Early-Onset Fetal Growth Restriction A Randomized Clinical Trial. JAMA Network Open. 2020;3(6):e205323. doi:10.1001/jamanetworkopen.2020.5323
[25] Maki S, et al. Tadalafil treatment for fetus with early onset growth restriction (TADAFER): a multicenter phase II trial. Am J Obstet Gynecol. 2019; 220:1 Suppl S257-S258.
[26] Maki S., Tanaka H., Tsuji M., Furuhashi F., Magawa S., Kaneda M.K., Nii M., Tanaka K., Kondo E., Tamaru S., Ogura T., Nishimura Y., Endoh M., Kimura T., Kotani T., Sekizawa A., Ikeda T. Safety evaluation of tadalafil treatment for fetuses with early-onset growth restriction (TADAFER): Results from the phase II trial. Journal of Clinical Medicine 2019 8:6

Reference ID: 4686961

evaluated the primary and secondary outcomes that they had set before the start of the trial using a post hoc analysis.

- Maki et al.[27] conducted a retrospective cohort study to evaluate the developmental progress of 24 (1.5-year old) infants whose mothers had taken tadalafil during pregnancy for IUGR. The authors found 21 and 20 out of 24 cases, respectively, attained body weight and height similar to those of age-matched normal infants and all cases caught up in head circumference. The authors concluded the growth and development of infants born to tadalafil treated mothers seemed to show good progress at a corrected age of 1.5 years.

- A study with 9 pregnant women with diagnosis of IUGR (EFW ≤ -1.5 SD and growth arrest for 2 weeks) were treated with tadalafil in a dose escalating trial (1 patient was administered 10mg/day, 5 patients were administered 20mg/day, 3 patients were administered 40mg/day) starting 22-30 week of gestation. Three patients were diagnosed with preeclampsia. Maternal serum placental growth factor was measured to predict efficacy of tadalafil. PIGF level increased. Median age of deliver was 36 weeks with a median birth weight of 1784 g. Median Apgar scores at 5 min was 9. Three cases were respiratory distress syndrome and one case of pulmonary hemorrhage were present. No other adverse fetal outcomes reported.[28]

In the last decade or so, there has been growing interest in the use of PDE5 inhibitors in the treatment of pregnancies with IUGR because it has been hypothesized that their vasodilatation activity may affect utero-placental circulation and perfusion resulting in improved gas and nutrient delivery and improved fetal growth.[29] Many studies were conducted in IUGR pregnancies, especially with sildenafil. Recent publication of the Dutch STRIDER trial questions the safety of sildenafil-use in pregnancy.[29] This randomized controlled trial consists of 216 IUGR pregnancies with 2 arms, one treated with sildenafil (25mg three times per day until 32 weeks or delivery), and another arm treated with placebo. This trial was stopped early due to lack of efficacy as well as safety concerns of increased neonatal death and increased cases of neonatal pulmonary hypertension in the treatment arm. DPMH reviewed the STRIDER Trial in a separate review. DPMH concluded that "it is unclear if the increase in neonatal pulmonary hypertension is due to sildenafil exposure… Current data are limited to individual arms for STRIDER and a meta-analysis including the pooled data from all the arms of the STRIDER trial are pending…. It is unclear if the data from the STRIDER trial can be generalized to pregnant women using this product due to PAH" The reader is referred to the DPMH review by Wenjie Sun, MD from October 5, 2020 for further details.[30]

---

[27] Maki S., Kato I., Enomoto N., Takakura S., Nii M., Tanaka K., Tanaka H., Hori S., Matsuda K., Ueda Y., Sawada H., Hirayama M., Sudo A., Ikeda T. Developmental evaluation of infants who have received tadalafil in utero for fetal growth restriction. Journal of Clinical Medicine 2020 9:5.

[28] Kubo-Kaneda M., Tanaka H., Maki S., Nii M., Umekawa T., Osato K., Kamimoto Y., Kondo E., Ikeda T. Placental growth factor as a predictor of the efficacy of tadalafil treatment for fetal growth restriction. Journal of Maternal-Fetal and Neonatal Medicine 2019; 32(17):2879-2882.

[29] Pels A, et al. Maternal Sildenafil vs Placebo in Pregnant Women with Severe Early-Onset Fetal Growth Restriction A Randomized Clinical Trial. JAMA Network Open. 2020;3(6): e205323. doi:10.1001/jamanetworkopen.2020.5323

[30] DPMH review of Revatio (sildenafil) NDAs 21845, 203109, 22473 by Wenjie Sun, MD on October 15, 2020. DARRTS Reference ID 4680974

Reference ID: 4686961

The safety concerns observed with sildenafil have not been seen with tadalafil exposure. Some studies suggest there may be some differences between the effects of tadalafil and sildenafil on pregnancies. Walton RB et al.[31] reported that sildenafil citrate improved pre-constricted placental-fetal arterial perfusion in a human placental model, whereas tadalafil produced no response. In addition, tadalafil improved the width of the maternal blood sinuses in the placenta of preeclampsia model mice but did not significantly change the fetal capillaries.[32] These observations suggest that tadalafil functions only on the maternal side, not on the fetal side.[33]

Reviewer comment:
Although there are safety concerns (neonatal mortality and neonatal pulmonary hypertension) with sildenafil, another PDE5 inhibitor, and use in pregnancy, sildenafil data might not be applicable to tadalafil. Studies that have been done with human placenta models and mice suggest that while sildenafil crosses the placenta, tadalafil does not cross the placenta.

Micromedex[20] states "there are no data with the use of tadalafil in pregnant women to determine a drug-associated risk for adverse developmental outcomes and gives the pregnancy rating: Fetal risk cannot be ruled out.

ReproTox[21] states "tadalafil treatment in pregnancies with fetal growth restriction was associated with improved fetal growth, decreased cesarean section for abnormal fetal heart rate tracings, prolonged pregnancy, and decreased fetal death."

Reviewer comment:
The published literature on tadalafil use in pregnancy consists of mostly tadalafil use in treatment of fetal growth restriction or preeclampsia. There are sparse data of tadalafil use during the first trimester limited to one case report. As described previously, nonclinical toxicology studies did not identify any concerns for adverse effects of tadalafil in pregnancy.

Overall, the applicant provided an adequate review of published literature regarding tadalafil use in pregnancy. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION
Nonclinical Experience
Tadalafil and/or its metabolites are present in the milk of lactating rats at concentrations approximately 2.4-times that found in the plasma.

The reader is referred to the full Pharmacology/Toxicology review by John Koerner, Ph.D. on March 6, 2009.

[31] Walton RB, et al. Evaluation of Sildenafil and Tadalafil for Reversing Constriction of Fetal Arteries in a Human Placenta Perfusion Model. Hypertension 2018;72(1): 167-176.
[32] Yoshikawa, K.; Umekawa, T.; Maki, S.; Kubo, M.; Nii, M.; Tanaka, K.; Tanaka, H.; Osato, K.; Kamimoto, Y.; Kondo, E.; et al. Tadalafil improves L-NG-nitroarginine methyl ester-induced preeclampsia with fetal growth restriction-like symptoms in pregnant mice. Am. J. Hypertens 2017, 31, 89–96.
[33] Maki S, et al. Safety evaluation of tadalafil treatment for fetuses with early-oncent grwoth restriction (TADAFER): Results from the Phase II trial. J Clin Med 2019; 8: 856. doi:10.3390/jcm8060856

Reference ID: 4686961

Review of Clinical Trials
There were no lactating women present in the clinical trials.

Review of Literature
Applicant's Review of Literature
The applicant conducted an online search of published literature regarding the use of tadalafil during lactation. The applicant found no relevant publications regarding tadalafil use and lactation.

The applicant concluded:

> "Tadalafil or its metabolites are excreted into rat milk... No relevant studies were found to provide evidence that tadalafil is safe for use in breastfeeding mothers. (b) (4)

DPMH's Review of Literature
In the 2019 DPMH review of tadalafil by Catherine Roca, MD,[4] DPMH noted:

> "There are no data on tadalafil in breast milk, effects on the breastfed infant, or effects on milk production."

DPMH conducted an updated published literature review, since 2019, in PubMed and Embase using the search terms "tadalafil" AND "lactation" and "tadalafil" AND "breastfeeding";

- No additional articles were found.

Lactmed[34] states "no published information is available on the use of tadalafil during breastfeeding. An alternate agent may be preferred." ReproTox[35] notes that tadalafil or a metabolite was present in rat milk at concentrations approximately 2.4-fold greater than that measured in plasma.[36] Hale[37] states "this product is not overtly hazardous and minimal levels in milk would probably be tolerated by an infant." Hales[37] rates tadalafil as "L3-No Data-Probably Compatible." Micromedex[38] gives "Lactation Rating: Infant risk cannot be ruled out." Tadalafil is not listed in Brigg's.[39]

---

[34] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 8/7/20.
[35] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/7/2020.
[36] Eli Lilly and Company. 2017. Adcirca prescribing information. Available at https://dailymed nlm.nih.gov/dailymed/drugInfo.cfm?setid=ff61b237-be8e-461b-8114-78c52a8ad0ae
[37] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.
[38] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 8/7/2020.
[39] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 8/7/20

Reference ID: 4686961

Reviewer comment:
Tadalafil concentrates in animal milk. Drug concentration in animal milk does not predict drug concentration in human milk, although when a drug is present in animal milk it is likely to be present in human milk. There are no data on the presence of tadalafil in human milk, its effect on the breastfed infant or milk production.

Overall, the applicant provided an adequate review of published literature regarding tadalafil use in lactating women. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of tadalafil up to 400 mg/kg/day, a dose producing AUCs for unbound tadalafil of 6–fold for males or 17-fold for females the exposures at the MRHD of 40 mg. In beagle dogs given tadalafil daily for 3 to 12 months, there was treatment-related non-reversible degeneration and atrophy of the seminiferous tubular epithelium in the testes in 20–100% of the dogs that resulted in a decrease in spermatogenesis in 40–75% of the dogs at doses of ≥10 mg/kg/day. Systemic exposure (based on AUC) at no-observed-adverse-effect-level (NOAEL) (10 mg/kg/day) for unbound tadalafil was similar to that expected in humans at the MRHD of 40 mg.

There was no treatment–related testicular findings in rats or mice treated with doses up to 400 mg/kg/day for 2 years.

The reader is referred to the full Pharmacology/Toxicology review by John Koerner, Ph.D. on March 6, 2009.

Review of Clinical Trials

There were no cases of infertility present in the clinical trials.

Review of Literature

Applicant's Review of Literature

The applicant conducted an online search of published literature regarding the use of tadalafil during lactation. For full account of applicant's submission of review of literature in lactation, see applicant's submission on July 27, 2020, Module 1.14, under "Review of Pregnancy, Lactation, and Reproductive Potential" (sequence number 003). Several publications of interest are listed below:

- A meta-analysis including eleven studies with 1,317 participants evaluated the effect of PDE 5 inhibitors on sperm parameters. In infertile men, acute administration of PDE 5 inhibitors had no effect on semen volume; however, the percentage of motile spermatozoa, total progressive motility, morphologically normal spermatozoa, and rapid progressive motility were increased after treatment with oral PDE 5 inhibitors. These changes were not observed in normal subjects. Therefore, in this systemic review, the

Reference ID: 4686961

authors conclude that oral PDE 5 inhibitors, such as tadalafil, could modestly increase sperm motility and morphology in infertile men.[40]

- A systematic review of the effects of PDE-5 inhibitors (sildenafil, vardenafil, tadalafil, and avanafil) highlights the potential implications of low-dose long-term use. The author concludes that many studies demonstrated a significant increase in sperm motility and viability both *in vivo* and *in vitro* at low concentrations, which was reduced at high concentrations.[41]

- An *in vitro* study of 70 asthenozoospermic human semen specimens were exposed to three different concentrations of tadalafil (4.0, 1.0, 0.5, 0 mg/mL) then examined at 0, 0.5, 1, 2, and 3 hours. Sperm samples treated with 4 mg/mL tadalafil solution demonstrated a significant decrease in sperm motility compared with the control samples; whereas, sperm samples treated with 1.0 or 0.5 mg/mL tadalafil solution demonstrated a significant increase in sperm progressive-forward motility. The authors suggest that the concentration of tadalafil plays an important role in the degree of sperm enhancement.[42]

- A study with 20 asthenozoospermic and 20 control normozoospermic patients examined the effect of tadalafil on sperm parameters. The authors determined that acute on-demand administration of tadalafil had no adverse effects on semen parameters.[43]
    - For the *in vitro* part of the study, 0.5 mL solutions with different tadalafil concentrations were added (0.2, 0.1, 0.05 and 0.025 μg/mL, respectively) to semen samples and examined after 0.5, 1, 2 and 4 hours. In both asthenozoospermic and normozoospermic samples treated with 0.2 μg/mL tadalafil had significantly increased sperm motility after 2 h incubation.
    - For the *in vivo* part of the study, oral administration of tadalafil (20 mg) or sildenafil (100 mg) was given to 10 asthenozoospermic and 10 control normozoospermic patients. In both groups, computer-assisted semen analysis parameters showed no significant difference. After the administration of tadalafil (2 h) and sildenafil (1 h), there was no significant difference observed in premature acrosome reaction incidence rate.

- In a study of 27 men between the ages of 19 and 35 suffering from psychogenic erectile dysfunction (ED), Corvasce et al. [44] found that the administration of once-daily tadalafil (5 mg) for 3 months resulted in an average increase of total number of sperm cells, the

[40] Tan P, Liu L, Wei S, Tang Z, Yang L, Wei Q. The effect of oral phosphodiesterase-5 inhibitors on sperm parameters: a meta-analysis and systematic review. Urology. 2017; 105:54-61.
[41] Mostafa T. Useful implications of low-dose long-term use of PDE-5 inhibitors. Sexual Medicine Reviews. 2016;4(3):270-284.
[42] Mostafa T. Tadalafil as an in vitro sperm motility stimulant. Andrologia 2007; 39(1): 12-15.
[43] Yang Y, Ma Y, Yang H, et al. Effect of acute tadalafil on sperm motility and acrosome reaction: in vitro and in vivo studies. Andrologia. 2014;46(4):417-422.
[44] Corvasce A, Albino G, Leonetti T, Buonomo AF, Marucco EC. Once-a-day tadalafil administration improves the spermogram parameters in fertile patients. The Archivio Italiano Di Urologia, Andrologia: Organo Ufficiale [di] Societa Italiana Di Ecografia Urologica e Nefrologica. 2015;87(3):210-213.

Reference ID: 4686961

percentage of nemasperms, and semen volume. No safety issues were reported, and the authors concluded that tadalafil (5 mg/day) had positive effects on spermatogenesis.

The applicant concluded:

> "Clinical and nonclinical studies suggest that tadalafil does not result in adverse effects on the fertility of men and there are no studies examining the impact of tadalafil on females of reproductive potential. The Tadliq package insert will include all information from the fertility section of the Adcirca package insert and no additional information will be added."

DPMH's review of literature

In the 2019 DPMH review of tadalafil by Catherine Roca, MD,[4] DPMH noted:

> "There is no evidence for adverse effects on female fertility or hormonal contraceptives with tadalafil. Data in both human and animal studies on the effects on male fertility are inconclusive."

DPMH conducted an updated published literature review, since 2019, using Embase, Pubmed, Micromedex,[45] ReproTox,[46] and TERIS.[47] Search terms used were "tadalafil AND reproduction," "tadalafil AND infertility," and "tadalafil AND contraception."

- No additional articles were found.

Reviewer comment:
Based on review of the available literature, there are no studies that suggest that tadalafil adversely affects female fertility. However, there is conflicting evidence in animal and human data on tadalafil's effect on spermatogenesis, sperm motility, and sperm concentration. No studies have been conducted to assess the actual effect of tadalafil on male fertility.

Overall, the applicant provided an adequate review of published literature regarding tadalafil use in males and females of reproductive potential. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Available data from randomized controlled trial observational studies, and case series with tadalafil use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. However, most of the data that describe tadalafil exposure are limited to the second and third trimesters of pregnancy; and therefore, are insufficient to assess a drug related risk of major birth defects and miscarriage. In animal reproduction studies, no adverse developmental effects were observed with oral administration of tadalafil to pregnant rats and mice during organogenesis at exposures 7X the maximum recommended human dose (MRHD).

[45] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 8/7/2020
[46] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/7/2020.
[47] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 8/7/2020

Reference ID: 4686961

Tadalafil is used in females of reproductive potential and in pregnancy. Although there is scarce data on tadalafil use during the first trimester of pregnancy in humans, it has been marketed in US for seventeen years, and there has not been a safety signal identified on use in pregnancy. In addition, based on animal study, there is no concern over tadalafil use and risk of major birth defects and miscarriage. Therefore, DPMH does not recommend a postmarking pregnancy study at the current time. If a safety issue should arise with regard to tadalafil use during pregnancy in the future, DPMH would recommend the division consider a single-arm pregnancy safety study.

Lactation

There are no data on the presence of tadalafil in human milk, the effects on the breastfed infant child or the effects on milk production. Tadalafil and/or its metabolites are present in the milk of lactating rats at concentrations approximately 2.4 times greater than that amount found in the plasma. Tadalafil concentrates in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is unknown if tadalafil concentrates in human milk.

Although there are concerns over whether or not tadalafil concentrates in human milk, tadalafil has been marketed in US for seventeen years and there have not been any concerning reports of tadalafil use during lactation in the published literature. DPMH does not recommend a postmarking lactation study at the current time.

Females and Males of Reproductive Potential

There is no evidence suggesting tadalafil adversely affects female fertility. There is conflicting evidence in animal and human data on tadalafil's effect on spermatogenesis and sperm motility. There is no study on tadalafil's effect on male fertility. Previous published studies were at a lower dose than the dose recommended for PAH. There are no reported drug to drug interaction (DDI) between tadalafil and hormonal birth control.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH recommendations are below and reflect the discussions with Division of Cardiovascular and Nephrology. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX A. Summary of Studies in previous DPMH Reviews of Tadalafil use in Pregnancy[48] (Reviewer's Table)

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
Sakamoto M, et al.[49] 2016 Japan	Case report	41-year-old pregnant woman with oligohydramnios and severe fetal growth restriction	Tadalafil 20mg/day From 22 weeks' gestation through delivery.	Increased amniotic fluid and increased fetal weight. Infant born by cesarean delivery at 32 weeks' gestation with Apgar scores of 5 and 7. No adverse effects were seen in the infant at age 3 months.	Mother was otherwise healthy and did not have PAH
Katsurahgi S, et al.[50] 2019 Japan	Retrospective case series	15 pregnant women with Eisenmenger syndrome with PAH	In one case, a pregnant woman received tadalafil 20mg/day at 15 weeks then 40 mg/day beginning at 23 weeks' gestation	10 women chose to terminate their pregnancies. 5 pregnancies continued to delivery. In the case where tadalafil was administered during pregnancy, fetal growth was normal. The remaining cases had small-for-gestational age infants.,	
Maki S, et al.[51] 2019 Japan	Prospective, randomized phase II trial (conventional treatment vs treatment with tadalafil 20 mg/day)	89 cases of pregnant women with fetal growth restriction	Tadalafil 20 mg/day until delivery (gestational age therapy began varied depending on when the diagnosis of fetal growth restriction was made)	Tadalafil did not significantly increase fetal growth velocity. Infant outcomes not described.	The trial was stopped because a trial in the UK (STRIDER) using sildenafil showed no improvement in early onset fetal growth restriction
Hohmann C, et al.[52] 2019 Germany	Case report	28-year-old pregnant woman with PAH	Tadalafil and ambrisentan prior pregnancy; ambrisentan discontinued once	At 32 weeks' gestation, patient had increasing cardiac symptoms; an emergency cesarean was	

[48] DPMH review of ADCIRCA (tadalafil), NDA 22332, by Catherine Roca, MD, on May 31, 2019, DARRTS Reference ID 4441500

[49] Sakamoto M, et al. Early-onset fetal growth restriction treated with the long-acting phosphodiesterase-5 inhibitor tadalafil: a case report. J Med Case Rep. 2016:10(1):317.

[50] Katsurahgi S, et al. Maternal and fetal outcomes in pregnancy complicated with Eisenmenger Syndrome. Taiwanese J Obstet Gynecol. 2019;58(2):183-187

[51] Maki S, et al. Tadalafil treatment for fetus with early onset growth restriction (TADAFER): a multicenter phase II trial. Am J Obstet Gynecol. 2019; 220:1 Suppl S257-S258.

[52] Hohmann C, et al. High-risk pregnancy in a patient with pulmonary arterial hypertension due to congenital heart disease (PAH_CHD) with temporary shunt inversion and deoxygenation. Pulm Circ 2019;9(2):1-4.

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
			pregnancy discovered, tadalafil continued throughout pregnancy	performed, and a healthy infant was delivered	
Kubo M, et al.[53] 2017 Japan	Prospective, open-label, phase-1 clinical trial	Twelve pregnant women ages ≥20 years old with a diagnosis of fetal growth retardation	-Tadalafil up to 20 mg/day; six cases were treated with tadalafil 40 mg/day. -Treatment initiated at gestational age 22 weeks or later.	One case of intrauterine fetal death at 36 weeks' gestation due to velamentous insertion of the umbilical cord	Serum concentration of tadalafil in cord blood was approximately ¼ that of maternal serum concentrations.
Tanaka H, et al. 2017 Japan	Case report	22-year-old primigravida with dichorionic diamniotic twin pregnancy and fetal growth restriction	Tadalafil 20mg/day beginning at 23 weeks' gestation	Cesarean section delivery, infants without adverse effects	
Tanaka H, et al.[54] 2017 Japan	Case report	35-year-old primigravida with severe pre-eclampsia and fetal growth restriction	Tadalafil 40 mg/day beginning at 27 weeks' gestation	-Temporary (2 week) improvement in pre-eclampsia -Infant delivered at 29 weeks' gestation and briefly admitted to neonatal intensive care, but overall had no major complications	
Kubo M et al.[55] 2017 Japan	Retrospective case-control study	11 pregnant women with fetal growth restriction treated with tadalafil compared to 14 pregnant women receiving conventional treatment for fetal growth restriction	Tadalafil doses ranging from 10-20 mg/day Median gestational age at enrollment = 31 weeks' gestation	Duration of pregnancy was >3 weeks longer in the tadalafil group, cesarean delivery was 2x greater in the conventional treatment group, and respiratory distress was greater in the	Small sample size, retrospective chart review

[53] Kubo M, et al. Safety and dose-finding trial of tadalafil administered for fetal growth restriction: a phase-1 clinical study. J Obstet Gynaecol Res. 2017;43(7):1159-1168.
[54] Tanaka H, et al. Treatment using tadalafil for severe pre-eclampsia with fetal growth restriction. J Obstet Gynaecol Res. 2017;43(7):1205-1208.
[55] Kubo M, et al. Retrospective study of tadalafil for fetal growth restriction: impact on maternal and perinatal outcomes. J Obstet Gynaecol Res. 2017;43(2):291-297.

Reference ID: 4686961

Publication; author/date/ Country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; drug/dose	Outcomes	Comments
				conventional treatment group ($p<0.05$)	

Reference ID: 4686961

Other cases of Tadalfil use in Pregnancy (Sponsor's table)[56]

Table 4. Summary of Studies with PDE5i Use Among Pregnant Women with PAH

Author (Year)	Location	Study design	Patients exposed to PDE5i (N)	PDE5i Dose	Gestational age at 1st PDE5i exposure (Weeks)	Pregnancy outcome	Gestational age at delivery (weeks)	Foetal /infant deaths	PTD	LBW	FGR	Neonatal Distress*	Congenital anomalies
Sildenafil													
Zhang (2018)	China	Case series	14	37.5mg/d to 75mg/d		Therapeutic abortion =7 Elective CS= 7		0	7	6	NR	4	NR
Xiang (2018)	China	Case study	1	25mg tid	32	Elective CS	Near term	NR	NR	NR	NR	NR	NR
Kawabe (2018)	Japan	Case study	1	60mg/d	6	Elective CS	28	0	1	0	NR	1	NR
Herrero (2018)	US	Case study	2	20mg tid	38, 35	SVD=1 Elective CS=1	38	0	NR	NR	NR	NR	NR
Daimon (2017)	Japan	Case study	2	60mg/d	Preconception=2	Elective CS=2	29, 30	0	3		0	0	0
Horng (2016)	US	Case study	1	20mg tid	24	CS	32	0	1	0	0	0	NR
Gerede (2015)	Turkey	Case study	2	60mg tid to 70mg tid	Preconception = 1; 28 weeks =1	Elective CS	32=1	0	1	NR	NR	1	NR
Rathod (2014)	India	case report	1	NR	Preconception	Elective CS	37	0	0	1	NR	0	NR
Cartago (2014)	Philippines	Case report	2	50mg tid	34, 35	Elective CS=1 SVD=1	34	0	2	1	NR	NR	NR
Timofeev (2015)	US	Case report	1	NR	2nd trimester to 23 weeks	Induced VD	36	1-SID	1	NR	NR	0	NR

Author (Year)	Location	Study design	Patients exposed to PDE5i (N)	PDE5i Dose	Gestational age at 1st PDE5i exposure (Weeks)	Pregnancy outcome	Gestational age at delivery (weeks)	Foetal /infant deaths	PTD	LBW	FGR	Neonatal Distress*	Congenital anomalies
Sildenafil, continued													
Duarte (2013)	US	Retrospective case series	4	NR		0		NR	NR	NR	NR	NR	NR
Albackr (2013)	Saudi Arabia	Case report	1	50mg tid	32	Induced VD		0	1	NR	NR	NR	NR
Subbaiah (2013)	India	Case series	4	20mg tid				0	NR	NR	NR	NR	0
Rosengarten (2012)	Israel	Case series	5	NR		CS		0	5	NR	NR	NR	NR
Ng (2012)	Singapore	Case report	1	25mg tid	35	SVD		0	1	NR	NR	NR	NR
Jais (2012)	Europe USA and Australia	Case series	7	NR				NR	NR	NR	NR	NR	NR
Smith (2012)	US	Case series	3	20mg tid	Preconception=1 25, 35	CS=2 VD=1	30, 36, 37	0	2	NR	NR	NR	NR
Curry (2012)	UK	Retrospective case series	9	NR=2				0	3	NR	1	NR	NR

[56] DPMH review of ADCIRCA (tadalafil), NDA 22332, by Catherine Roca, MD, on May 31, 2019, DARRTS Reference ID 4441500

Reference ID: 4686961

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WENJIE SUN
10/16/2020 10:20:57 AM

MIRIAM C DINATALE
10/16/2020 10:40:30 AM

LYNNE P YAO
10/19/2020 06:25:58 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 24, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214522
Product Name, Dosage Form, and Strength:	Tadliq (tadalafil) suspension, 20 mg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CMP Development LLC
FDA Received Date:	April 23, 2020 and July 27, 2020
OSE RCM #:	2020-895
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

Reference ID: 4675472

1 REASON FOR REVIEW

CMP Development LLC submitted NDA 214522 Tadliq (tadalafil) suspension on April 23, 2020. Tadliq is proposed for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. We reviewed the proposed container label, Prescribing Information (PI), and Patient Information for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, PI, and patient information for Tadliq (tadalafil) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the PI, container label, and patient information identified areas that can be modified to improve the clarity of the information presented. We note that there is a graphic design present on the container label that appears to be part of the proprietary name and competes in prominence with the proprietary name that may contribute to medication errors. The established name is not at least ½ the size of the proprietary name. We note that the "Rx Only" statement competes in prominence with the net quantity. The manufactures' logo "CMP PHARMA" competes in prominence with important information on the principal display panel. It is also redundant as it is present on the side panel. We provide recommendations for the division in Section 4.1 and recommendations for CMP Development in Section 4.2 below.

Reference ID: 4675472

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the division in Section 4.1 and recommendations for CMP Development in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. We recommend removing the statement in Dosage and Administration (b) (4) to prevent confusion. The frequency is already described as once daily and thus describing (b) (4) may cause confusion especially if someone misses the word (b) (4)
2. The strength statement should be presented as specified amount per 5 mL per USP General Chapter (7) labeling and for consistency with the container labeling. We recommend revising the strength statement to "Oral Suspension: 20 mg/5 mL".

B. Full Prescribing Information

1. We recommend removing the statement (b) (4) to prevent confusion. The frequency is already described as once daily and thus describing (b) (4) may cause confusion especially if someone misses the word (b) (4).
2. We recommend revising the section headings for appropriateness. Revise 2.1 to "Recommended Dosage", 2.2 to "Dosage Modifications for Renal Impairment" and 2.3 to "Dosage Modifications for Hepatic Impairment", and 2.4 to "Dosage Modification due to Concomitant Medication".
3. The strength statement in Dosage Forms and Strengths should be presented as specified amount per 5 mL per USP General Chapter (7) labeling and for consistency with the container labeling. We recommend revising the strength statement to "Oral Suspension: 20 mg/5 mL as white to off-white opaque suspension".

4.2 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. As currently presented the graphic competes in prominence with the proprietary name and other important information on the principal display panel (PDP). Ensure that the graphic does not compete in prominence with the pertinent information on the PDP.
2. As currently presented the established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3. Decrease the prominence and relocate the statement "Rx Only" as this information appears more prominent than the net quantity on the principal display panel.
4. To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read "Recommended Dosage: See prescribing information."
5. Consider decreasing the manufacturer information as currently presented it clutters the principal display panel and takes readers' attention away from important information such as proprietary and proper names and strength.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tadliq received on April 23, 2020 from CMP Development LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Tadliq and the Listed Drug

Product Name	**Tadliq**	**Adcirca**[a]
Initial Approval Date	N/A	May 22, 2009
Active Ingredient	tadalafil)	tadalafil
Indication	Tadliq is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.	ADCIRCA is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.
Route of Administration	oral	oral
Dosage Form	suspension	tablet
Strength	20 mg/5 mL	20 mg
Dose and Frequency	40 mg (10 mL) once daily	40 mg once daily
How Supplied	TADLIQ (tadalafil) Oral Suspension, 40 mg/10 mL is a white to off-white, opaque, peppermint-flavored suspension. It is available in a 150 mL bottle (NDC 46287-045-15)	ADCIRCA (tadalafil) is supplied as follows: 20 mg orange, film–coated, almond–shaped tablets (not scored), debossed with "4467" Bottles of 60 NDC 66302-467-60
Storage	Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Shake well before use.	Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep out of reach of children.
Container Closure	Tadalafil Oral Suspension, 4 mg/mL is packaged in 150 mL (b) (4) bottle (b) (4)	HDPE bottle with a silica gel dessicant.

[a] Adcirca [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2017 May 5. Available from: https://www.accessdata fda.gov/drugsatfda_docs/label/2017/022332s009lbl.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Tadliq labels and labeling submitted by CMP Development LLC.

- Container label received on April 23, 2020
- Prescribing Information (Image not shown) received on July 27, 2020, available from \\CDSESUB1\evsprod\nda214522\0003\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi.pdf.

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
09/25/2020 11:14:13 AM

HINA S MEHTA
09/29/2020 10:56:21 AM