CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214952Orig1s000

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:	April 27, 2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214952
Product Name, Dosage Form, and Strength:	Liqrev (Sildenafil) Oral Suspension, 10 mg/mL
Applicant/Sponsor Name:	CMP Development LLC
TTT ID #:	2022-1217-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on April 25, 2023 for Liqrev. We reviewed the revised container label for Liqrev (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.

[a] Kundreskas, Jody. Label and Labeling Review for Liqrev (NDA 214952). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 DEC 01. TTT ID No.: 2022-1217.

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JODY K KUNDRESKAS
04/27/2023 03:16:18 PM

HINA S MEHTA
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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:	February 2, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214952
Product Name and Strength:	Liqrev (Sildenafil) Oral Suspension, 10 mg/mL
Applicant/Sponsor Name:	CMP Development LLC (CMP)
OSE RCM #:	2020-2094-2
DMEPA 2 Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

CMP submitted a response to the Complete Response (CR) on October 29, 2021 for NDA 214952 Liqrev (sildenafil) oral suspension. NDA 214952 received a CR on August 05, 2021 due to facility inspection issues. As part of the response to complete response, CMP referenced the container label previously submitted on June 30, 2021.

2 CONCLUSION

We find the container label acceptable from a medication error perspective and we have no additional recommendations at this time.

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MAXIMILIAN STRAKA
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HINA S MEHTA
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LABEL AND LABELING REVIEW
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)

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Date of This Review:	12/01/2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214952
Product Name, Dosage Form, and Strength:	Liqrev (Sildenafil) Oral Suspension, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CMP Development LLC
FDA Received Date:	06/30/2021 and 08/29/2022
TTT ID #:	2022-1217
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

CMP Development LLC submitted a response to Complete Response for NDA 214952 Liqrev (sildenafil) oral suspension 10 mg/mL. We reviewed the proposed Liqrev Prescribing Information (PI), Patient Information and container label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

The application for Liqrev (NDA 214952) was originally submitted on October 5, 2020, as a 505(b)(2) referencing product Revatio. Revatio was first approved June 3, 2005 as 20 mg tablets under NDA 021845. On November 18, 2009, Revatio injection 10 mg/12.5 mL was approved under NDA 022473. On August 30, 2012, Revatio 10 mg/mL for oral suspension was approved under NDA 203109.

Liqrev (NDA 214952) was issued a Complete Response for product quality issues on August 5, 2021. On October 29, 2021, the application for Liqrev was resubmitted and again received a Complete Response for product quality issues on April 28, 2022. The application for Liqrev was resubmitted on August 29, 2022 and is the subject of this review.

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
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 PI, container label and Patient Information for Liqrev oral suspension to identify deficiencies that may lead to medication errors and other

areas of improvement. We identified areas of the proposed PI, container label and Patient Information that could be revised to improve clarity and readability of important information. For the Division, we recommend adding clarifying statements to the PI and Patient Information. For the Applicant, we recommend adding Beyond Use Date information to the container label. We provide recommendations for the Division in section 4.1 and the Applicant in section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed PI, container label and Patient Information for Liqrev oral solution may be improved to promote the safe use of the product as described in sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. Dosage and Administration Section, Section 2
    a. We recommend adding the following statement to section 2: "A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately.".
2. How Supplied/Storage and Handling Section, Section 16
    a. We recommend revising the description of the formulation to include the packaging configuration of 122 mL.
3. Patient Counseling Information, Section 17
    a. We recommend adding the following statements to Section 17: "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy." We recommend this to decrease the risk of wrong dose error, particularly when measuring smaller doses.
4. Patient Information
    a. We recommend adding the following statement to "How should I take LIQREV?" section of the Patient Information: "Use an oral dosing syringe to correctly measure your dose. Ask your pharmacist for an oral dosing syringe if you do not have one.".

4.2 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC

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

A. Container Labels

1. We recommend including the statement “Date of first opening __/__/__. Discard unused portion 90 days after first opening.” in bold font on the side panel of the container label. The “__/__/__” statement will alert the users to write a complete date (month, day, and year) on the container label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Liqrev received on 06/30/2021 from CMP Development LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Liqrev and the Listed Drug		
Product Name	Liqrev	Revatio (NDA 021845, 022473, 203109)[a]
Initial Approval Date	N/A	06/03/2005
Active Ingredient	Sildenafil	Sildenafil
Indication	LIQREV is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when sildenafil was added to background epoprostenol therapy [see Clinical Studies (14)]. Studies establishing effectiveness were short-term (12 to 16 weeks) and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%). (b) (4)	REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO was added to background epoprostenol therapy [see Clinical Studies (14)]. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%). Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity [see Clinical Studies (14)].
Route of Administration	Oral	• Oral • Intravenous
Dosage Form	Oral Suspension	• Tablet

[a] REVATIO [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2018 FEB [accessed 11/15/2022]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021845s018lbl.pdf

		• Powder for Oral Suspension • Injection
Strength	10 mg/mL	• Tablets: 20 mg • Powder for Oral Suspension: 10 mg/mL (when reconstituted) • Injection: 10 mg/12.5 mL
Dose and Frequency	The recommended dose of LIQREV is (b) (4) 20 mg orally three times a day. (b) (4) (b) (4) Shake well for at least 10 seconds before use. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended.	• Tablets and Oral Suspension: The recommended dose of REVATIO is (b) (4) 20 mg three times a day. (b) (4) (b) (4) In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg three times a day is not recommended. See full prescribing information for reconstitution instructions for the Powder for Oral Suspension. • Injection: REVATIO injection is for the continued treatment of patients with PAH who are currently prescribed oral REVATIO and who are temporarily unable to take oral medication. The recommended dose is (b) (4) 10 mg administered as an intravenous bolus injection three times a day. The dose of REVATIO injection does not need to be adjusted for body weight. A 10 mg dose of REVATIO injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.
How Supplied	LIQREV(sildenafil) Oral Suspension 10 mg/mL is a white to off-white, opaque, strawberry-flavored suspension. It is available in an	• REVATIO tablets are supplied as white, film-coated, round tablets containing sildenafil citrate equivalent to the

	amber glass bottle with a child resistant tamper-evident cap (NDC 46287-055-01).	nominally indicated amount of sildenafil as follows: Bottle of 90 tablets (20 mg) NDC 0069-4190-68 Engraving on tablet: RVT20 • REVATIO powder for oral suspension is supplied in amber glass bottles. Each bottle contains white to off-white powders containing 1.57 g of sildenafil citrate (equivalent to 1.12 g sildenafil). Following constitution, the volume of the oral suspension is 112 mL (10 mg sildenafil/mL). A 2 mL oral dosing syringe (with 0.5 mL and 2 mL dose markings) and a press-in bottle adaptor are also provided. Powder for Oral Suspension – bottle 10 mg/mL (when reconstituted) NDC 0069-0336-21 • REVATIO injection is supplied as a clear, colorless, sterile, ready to use solution containing 10 mg sildenafil/12.5 mL presented in a single-use glass vial. Vial individually packaged in a carton 10 mg/12.5 mL NDC 0069-0338-01
Storage	Store from 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP for controlled room temperature]. Shake well before use for at least 10 seconds. Use the bottle within 90 days once it has been opened.	• Recommended Storage for REVATIO Tablets: Store at controlled room temperature 20°C -25°C (68°F -77°F); excursions permitted to 15°C - 30°C (59°F -86°F) [see USP Controlled Room Temperature]. • Recommended storage for REVATIO for oral suspension: Store below 30°C (86°F) in the

		original package in order to protect from moisture. Constituted Oral Suspension Store below 30°C (86°F) or in refrigerator at 2°C to 8°C (36° F - 46°F). Do not freeze. The shelf-life of the constituted oral suspension is 60 days. Any remaining oral suspension should be discarded 60 days after constitution. • Recommended Storage for REVATIO Injection: Store at controlled room temperature 20°C -25°C (68°F -77°F); excursions permitted to 15°C - 30°C (59°F -86°F) [see USP Controlled Room Temperature].
Container Closure	amber glass bottle with a child resistant tamper-evident cap	• Bottles of 90 tablets • Amber glass bottle intended for constitution, final volume after reconstituting is 112 mL (10 mg/mL) with press in bottle adaptor and 2 mL oral syringe provided • Single use glass vial for injection

APPENDIX B. PREVIOUS DMEPA REVIEWS

On 11/15/2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Liqrev', 'NDA 214952', and 'Revatio'. Our search identified 8 previous reviews[b,c,d,e,f,g,h,i], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Aidoo, Mariette. Label and Labeling Review for Liqrev (NDA 214952). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 1 OSE RCM 5. No.: 2020-2094.

[c] Aidoo, Mariette. Label and Labeling Memorandum for Liqrev (NDA 214952). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUL 2. OSE RCM No.: 2020-2094-1.

[d] Straka, Maximilian. Label and Labeling Memorandum for Liqrev (NDA 214952). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 FEB 2. OSE RCM No.: 2020-2094-2.

[e] Ford, Ray. Label and Labeling Review for Revatio (NDA 203109). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 MAY 2. OSE RCM No.: 2011-4482.

[f] Ford, Ray. Label and Labeling Memorandum for Revatio (NDA 203109). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 AUG 27. OSE RCM No.: 2011-4482-1.

[g] Holmes, Loretta. Label and Labeling Review for Revatio (NDA 203109/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 SEP 11. OSE RCM No.: 2013-1859.

[h] Thomas, Sarah. Label and Labeling Review for Revatio (NDA 203109/S-15). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 31. OSE RCM No.: 2019-1895.

[i] Thomas, Sarah. Label and Labeling Memorandum for Revatio (NDA 203109/S-15). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 21. OSE RCM No.: 2019-1895-1.

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,[j] along with postmarket medication error data, we reviewed the following Liqrev labels and labeling submitted by CMP Development LLC.

- Container label received on 06/30/2021
- Prescribing Information (Image not shown) received on 06/30/2021, available from \\CDSESUB1\EVSPROD\nda214952\0016\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi.pdf
  And
  \\CDSESUB1\EVSPROD\nda214952\0016\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi-track.pdf
- Patient Package Insert received on 06/30/2021, available from \\CDSESUB1\EVSPROD\nda214952\0016\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-ppi.pdf
  And
  \\CDSESUB1\EVSPROD\nda214952\0016\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-ppi-track.pdf

G.2 Label and Labeling Images

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

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/s/

JODY K KUNDRESKAS
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HINA S MEHTA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	July 2, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214952
Product Name and Strength:	Liqrev (Sildenafil) Oral Suspension, 10 mg/mL
Applicant/Sponsor Name:	CMP Development LLC (CMP)
OSE RCM #:	2020-2094-1
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

CMP submitted a revised container label received on June 30, 2021 for Liqrev (Sildenafil). We reviewed the revised container label for Liqrev (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.

[a] Aidoo, M. Label and Labeling Review for Liqrev (NDA 214952). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APRIL 9. RCM No.: 2020-2094.

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/s/

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HINA S MEHTA
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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:	May 3, 2021
To:	Christine Sadr, MS Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior 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):	LIQREV (sildenafil oral suspension)
Dosage Form and Route:	For oral use
Application Type/Number:	NDA 214952
Applicant:	CMP Development, LLC.

1 INTRODUCTION

On October 5, 2020, CMP Development, LLC., submitted for the Agency's review an original New Drug Application (NDA-214952) for LIQREV (sildenafil oral suspension), for oral use, proposing an indication of use in the treatment of pulmonary arterial hypertension (PAH) in adults to improve exercise ability and delay clinical worsening.

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 Cardiology and Nephrology (DCN) on December 2, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LIQREV (sildenafil oral suspension), for oral use.

2 MATERIAL REVIEWED

- Draft LIQREV (sildenafil oral suspension) PPI received on October 5, 2020 and received by DMPP and OPDP on April 23, 2021.
- Draft LIQREV (sildenafil oral suspension) Prescribing Information (PI) received on October 5, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 23, 2021.

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. In our review of the PPI the target reading level is at or below an 8th grade 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.

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/s/

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LASHAWN M GRIFFITHS
05/03/2021 01:35:23 PM

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

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

Memorandum

Date: April 30, 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 LIQREV® (sildenafil oral suspension)

NDA/BLA: 214952

In response to DCN consult request dated December 2, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and the carton and container labeling for LIQREV® (sildenafil 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 April 23, 2021, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DCN on April 23, 2021, 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.

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ZARNA PATEL
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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)

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Date of This Review:	April 15, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214952
Product Name, Dosage Form, and Strength:	Liqrev (Sildenafil) Oral Suspension, 10 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	CMP Development LLC
FDA Received Date:	October 5, 2020 and December 23, 2020
OSE RCM #:	2020-2094
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As a part of the approval process for 505(b)(2) NDA 214952 submission, this review evaluates the proposed Prescribing Information (PI), patient information sheet, and container labels for Liqrev (sildenafil) oral suspension.

1.1 BACKGROUND INFORMATION

The reference product REVATIO (sildenafil) tablet was approved under NDA 021845 on June 03, 2005. It is currently available as 20 mg tablets. On November 18, 2009 REVATIO (sildenafil) injection was approved under NDA 022473 in a strength of 10 mg/12.5 mL. On August 30, 2012 REVATIO (sildenafil) for oral suspension was approved as 10 mg/mL under NDA 203109.

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
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 submitted a 505(b)(2) NDA to obtain marketing approval for Liqrev (sildenafil) oral suspension, 10 mg/mL. Liqrev is proposed for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening.
We note that the proposed Liqrev (sildenafil) oral suspension has the same dosage regimen as the tablet and for oral suspension (b) (4) 20 mg three times a day, (b) (4) route of administration, and indication as the LD.

We performed a risk assessment of the proposed container label, prescribing information (PI) and patient information for Liqrev (sildenafil) to identify deficiencies that may lead to medication errors and areas for improvement. In Section 16 of the PI, CMP notes: “Shake well before use.” without providing a specified amount of time for which the product will need to be

shaken. After discussion with the Office of Pharmaceutical Quality (OPQ), it was determined the suspension needs to be shaken for 10 seconds.

We note the Revatio for oral suspension product contains an Instructions for Use (IFU) for patients. The IFU outlines the instructions on shaking the bottle and withdrawing the suspension based on the prescribed dose. We recommend the Division of Cardiology and Nephrology request CMP include an IFU for Liqrev.

We find the patient information sheet acceptable from a medication error perspective. Our review of the container label and prescribing information (PI) for Liqrev (sildenafil) oral suspension identified areas where the label and labeling may be improved to promote the safe use of the product. Thus, we provide related recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant.

4 CONCLUSION & RECOMMENDATIONS

The PI and container label can be improved from a medication error perspective. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. We note the Revatio for oral suspension product contains an Instructions for Use (IFU) for patients. The IFU outlines the instructions on shaking the bottle and withdrawing the suspension based on the prescribed dose. We recommend the Division request CMP include an IFU for Liqrev.

B. Highlights of Prescribing Information (HPI)

1. Dosage and Administration Section

a. As currently presented the recommended dosage frequency may be confusing as it describes two different frequencies. We defer to the division; however, our recommendation is as follows. In addition, we recommend removing the hyphen (-) between the frequency range and adding the route (i.e. orally) to the dosing information as currently presented the route of administration is missing.

i. Revise as follows: (b) (4) 20 mg orally three times a day. (b) (4)

C. Full Prescribing Information (FPI)

1. Dosage and Administration Section

a. We recommend adding the route (i.e. orally) to the dosing information as currently presented the route of administration is missing in Section 2.1: "The recommended dose of LIQREV is (b) (4) 20 mg orally three times a day."

b. We recommend replacing hyphen (-) between the frequency to read: (b) (4)

c. In addition, revise to include the statement 'Shake well for 10 seconds before use' of suspension product after the administration comment noted in (b) above.

2. How Supplied/Storage and Handling Section

a. As currently presented, there is a hyphen (-) in between the temperature ranges. In addition, the storage statement does not include a statement about shaking prior to administration to ensure equitable distribution of active ingredient in suspension formulation.
Revise the storage information to read:

i. Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). [See USP for controlled room temperature]. Shake well before use for 10 seconds.

4.2 RECOMMENDATIONS FOR CMP DEVELOPMENT LLC

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

B. Container Labels

1. To ensure consistency with the terminology in the Prescribing Information, revise the recommended dosage statement from (b) (4) (b) (4) to the following: "Recommended Dosage: See Prescribing Information" on the side panel.
2. Consider decreasing the prominence of the company name in the blue pictorial at the bottom of the Principal Display Panel to create less congestion and easy readability.
3. The statement "Rx Only" appears in bold on the top right corner of the PDP. We recommend debolding "Rx only" as currently presented it is competing in prominence with other information on the principal display panel.
4. As currently presented, the established name depicts the placement of the dosage form (i.e. oral suspension) inside the parenthesis with the established name. Revise the established name to read: " (sildenafil) oral suspension." for consistency with the prescribing information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Liqrev received on October 5, 2020 and December 23, 2020 from CMP Development LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Liqrev (sildenafil) suspension and the Listed Drug		
Product Name	**Liqrev (sildenafil)**	**Revatio (sildenafil)**[a] (NDA 021845)
Initial Approval Date	N/A	June 03, 2005
Active Ingredient	Sildenafil	
Indication	Approved for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening.	
Route of Administration	Oral	
Dosage Form	Oral Suspension (white opaque suspension with strawberry flavor)	•Tablets • Injection • For Oral Suspension)
Strength	10 mg/mL	Tablets: 20 mg • Injection: 10 mg /12.5 mL in a single use vial • For Oral Suspension: 10 mg/mL (when reconstituted)
Dose and Frequency	(b) (4) 20 mg three times a day. (b) (4) (b) (4)	•Tablets and oral suspension: (b) (4) (b) (4) 20 mg three times a day, (b) (4) (b) (4) see full prescribing information for reconstitution instructions for the Powder for Oral Suspension. • Injection: 2.5 mg or 10 mg three times a day administered as an intravenous bolus injection.
How Supplied	122 mL amber glass bottle with a child resistant tamper-evident cap.	- 20 mg tablet: Bottle of 90 - (b) (4)

[a] Revatio (sildenafil) [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 JAN 5. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021845s018lbl.pdf

Storage	Store at controlled room temperature 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]. Shake well before use.	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].
Container Closure	Glass bottle with a child-resistant closure.	Bottle package

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 11, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, sildenafil. Our search identified one previous review[b], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Thomas, S. Label and Labeling Review for Revatio (NDA 203109/S-15). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 31. RCM No.: 2020-1895.

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 Liqrev labels and labeling submitted by CMP Development LLC.

- Container label received on October 5, 2020
- Prescribing Information (Image not shown) received on October 5, 2020 and December 23, 2020, available from \\CDSESUB1\evsprod\nda214952\0003\m1\us\1-14-labeling\1-14-1-draft-labeling\1-14-1-3-draft-pi.doc

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/

MARIETTE A AIDOO
04/15/2021 12:13:50 PM

HINA S MEHTA
04/16/2021 02:44:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
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Division of Pediatric and Maternal Health Review

Date: 3/31/2021 **Date consulted:** 12/29/2020

From: Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

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

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

To: Division of Cardiology and Nephrology (DCN)

Drug: LIQREV (sildenafil oral suspension, 10 ng/mL)

NDA: 214952

Applicant: CMP Development, LLC

Subject: Pregnancy and Lactation Labeling

Indication: LIQREV is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. (b) (4)

(b) (4)

Materials Reviewed:

- Applicant's background package for NDA 214952
- DPMH review of REVATIO, NDA 21845, Catherine Roca, M.D., Medical Officer, September 22, 2017. DARRTS Reference ID 4157089
- DPMH review of Sildenafil TheRapy in Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER) trial results and possible labeling change for subsection 8.1, Wenjie Sun, MD, October 5, 2020. DARRTS Reference ID 4680974
- Division of Pharmacovigilance and Office of Pediatric Therapeutics review of Neonatal or Fetal Complications of Sildenafil, Thao Tran, PharmD, BPCS and Gerri Baer MD, January 18, 2019. DARRTS Reference ID 4378417
- Neonatal-Perinatal Medicine Consult Sildenafil STRIDER Trial Review, An N. Massaro MD, September 22, 2020. DARRTS Reference ID 4675048

Consult Question: "Please evaluate the submitted data on use/risks of sildenafil during pregnancy, lactation, and reproductive risks and comment on proposed labeling describing those risks (PLLR conversion) in the LIQREV label."

INTRODUCTION

On December 29, 2020, the DCN consulted the DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of LIQREV (sildenafil) labeling to comply with the Pregnancy and Lactation Labeling (PLLR) format.

REGULATORY HISTORY

- On October 5, 2020, the applicant submitted a 505(b)(2) NDA based on the reference drug, REVATIO (sildenafil), NDA 21845.
- The relied upon drug, REVATIO (sildenafil), a phosphodiesterase-5 (PDE-5) inhibitor, was originally approved in the U.S. under NDA 21845 on June 3, 2005, for the treatment of pulmonary arterial hypertension [World Health Organization (WHO) Group 1] to improve exercise ability and to decrease clinical worsening.
- REVATIO (sildenafil) labeling was converted to meet PLLR requirements on February 1, 2018. (DPMH consult for PLLR formatting completed on September 22, 2017.)
- A tracked safety issue (TSI) 1937 was opened in 2018 and was triggered by the Sildenafil TheRapy in Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER) trial results. In addition, a collaborative review was written between the Office of Pediatric Therapeutics (OPT) and the DPV-I evaluating the FDA Adverse Event Reporting System (FAERS) and medical literature cases of fetal or neonatal complications, particularly increased rates of persistent pulmonary hypertension in the neonate (PPHN) and neonatal death, associated with maternal exposure to sildenafil for approved indications as well as off-label use.
- On July 28, 2020, the DCN consulted DPMH to provide input on the relevance of a published article (Pels et al. 2020[1]), which described an increased risk of PPHN

[1] Pels A, et al., Maternal sildenafil vs placebo in pregnant women with severe early-onset fetal growth restriction: a randomized clinical trial. *JAMA Netw Open* 2020;3(6):e205323.

in infants exposed to sildenafil *in utero* during a treatment trial for severe early-onset fetal growth restriction, for subsection 8.1 of sildenafil labeling. DPMH recommended waiting to revise subsection 8.1 after data from a meta-analysis (expected to be published in 2021) can be reviewed.

BACKGROUND

LIQREV (sildenafil) Drug Characteristics[2]

Drug Class	Sildenafil is a phosphodiesterase type 5 (PDE-5) inhibitor.
Mechanism of action	Sildenafil increases cGMP within pulmonary vascular smooth muscle cells, causing relaxation. In patients with PAH this can result in vasodilation of the pulmonary vascular bed and, to a lesser degree, systemic vasodilation.
Molecular weight	666.7 Daltons
Dose	Oral suspension: (b) (4) 20 mg three times daily (b) (4)
Half-life	Terminal half-life for both sildenafil and its active metabolite is approximately 4 hours in healthy adult subjects.
Protein Binding	approximately~ 96%
Oral Bioavailability	Rapidly absorbed with a mean absolute bioavailability of 41%. Absorption is reduced when taken with a high fat meal.
Serious Adverse Reactions	• (b) (4) • Vasodilation effects may be more common in patients with hypotension or antihypertensive therapy. • Use in pulmonary veno-occlusive disease may cause pulmonary edema and is not recommended. • Hearing or visual impairment: seek medical attention if sudden decrease or loss of vision or hearing occurs. • Pulmonary hypertension secondary to sickle cell disease: LIOREV may cause serious vaso-occlusive crisis.

Current Labeling of Drug Relied Upon, REVATIO (sildenafil)[3]

Approved labeling is in Pregnancy and Lactation Labeling Rule format.
There is no boxed warning.
There is no warning for embryofetal toxicity.
Contraindications • Use with organic nitrates or riociguat • History of hypersensitivity to sildenafil or any component of the tablet, injection or oral suspension.
Subsection 8.1 Pregnancy Risk Summary

[2] LIQREV (sildenafil) proposed package insert
[3] REVATIO (sildenafil) approved package insert, Drugs@FDA, accessed 2/11/2021

Limited published data from randomized controlled trials, case-control studies, and case series do not report a clear association with sildenafil and major birth defects, miscarriage, or adverse maternal or fetal outcomes when sildenafil is used during pregnancy *(see Clinical Considerations).* Animal reproduction studies conducted with sildenafil showed no evidence of embryo-fetal toxicity or teratogenicity at doses up to 32- and 65- times the recommended human dose (RHD) of 20 mg three times a day in rats and rabbits, respectively *(see Data).* The estimated background risk of major birth defects and miscarriage for the indicated population 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 2-4% and 15-20%, respectively. Clinical Considerations *Disease-Associated Maternal and/or Embryo/Fetal Risk* Pregnant women with untreated pulmonary arterial hypertension are at risk for heart failure, stroke, preterm delivery, and maternal and fetal death. Data *Animal Data* No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m2 basis, 32- and 65- times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m2 basis).
Subsection 8.2 Lactation Risk Summary Limited published data from a case report describe the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Limited clinical data during lactation preclude a clear determination of the risk of REVATIO to an infant during lactation.
There are no pregnancy testing/contraception recommendations.
There are no listed adverse effects on hormonal contraception

REVIEW
PREGNANCY
Pulmonary Arterial Hypertension (PAH) and Pregnancy

PAH is associated with high maternal and fetal morbidity and mortality.[4] In *Guidelines for the diagnosis and treatment of pulmonary hypertension,*[5] it states that "pregnancy is associated with a risk to mother and fetus and should be discouraged. Should a PAH patient become pregnant, termination of the pregnancy should be discussed." Patients who choose to continue pregnancy should be treated with disease-targeted therapies, and elective delivery should be planned. A systemic review of all published reports from 1997 to 2007 found that overall maternal mortality was 17% in women with idiopathic PAH, 28% in PAH associated with congenital heart disease[6] and 33% in PAH of other etiologies.[7]

The causes of poor maternal outcomes include risk of death from right heart failure and stroke from intracardiac shunting.[8] 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.[4,9] The most common risk to the fetus is death.[10] In a publication describing pregnancy outcomes in women with PAH, the outcomes were considered poor with high rates of pre-term deliveries ranging from 85 to 100% and fetal growth restriction in up to one-third of pregnancies.[11]

Nonclinical Experience

The reader is referred to the Pregnancy section of the relied upon drug labeling and to the Nonclinical review by Xi Yang, PhD and Jean Wu, PhD.

Applicant's Review of Literature

The applicant performed a search of the published literature from September 1, 2017 through January 2021 using the PubMed database and the search terms, "sildenafil," and "pregnancy."

The studies located in this search were also located in the previous DPMH reviews. See Appendix A for a summary of these publications.

[4] Li Qiangqiang, et al. peripartum outcomes in a large population of women with pulmonary arterial hypertension associated with congenital heart disease. *Eur J Prev Cardiol*. 2019;26(10):1067-1076.
[5] Galie N, et al. 2015 ESC/ERS Guideline for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2015;46:903-975.
[6] Weiss BM *et al*. Outcome of pulmonary Vascular Disease in pregnancy: A Systematic Overview from 1978 through 1996. *J Am Coll Cardiol*. 1998; 31(7): 1650-1657.
[7] Bedard E *et al*. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J*. 2009; 30(3):256–65.
[8] 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.
[9] Jais X *et al*. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. *Eur Respir J* 2012; 40: 881–885.
[10] Gleicher N *et al*. Eisenmenger's syndrome and pregnancy. *Obstet Gynecol Surv* 1979; 34: 721–741.
[11] 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.

DPMH Review of Literature:
DPMH conducted an updated search of the literature from the time of the previous DPMH review[12] (October 4, 2020) to present using PubMed, Embase, Reprotox, and Micromedex[13] using the search terms, "sildenafil and pregnancy," "sildenafil and pregnant women," "sildenafil and pregnancy and birth defects," "sildenafil and fetal malformations," "sildenafil and stillbirth," and "sildenafil and miscarriage."

See Appendix A for previous literature reviews. To briefly summarize:

At the time of the DPMH PLLR review of REVATIO,[14] data from the published literature did not indicate an overall increased risk of major malformation, stillbirth, or neonatal death.

Data from the Dutch STRIDER Trial,[15] showed that

- Infants exposed to sildenafil *in utero* had an increased risk for developing pulmonary hypertension compared to infants exposed to placebo, (RR 3.67, 95% CI 1.28-10.51), p=0.0008).
- There was no difference in the composite primary outcome of perinatal mortality or major neonatal morbidity (intraventricular hemorrhage grade 3 or more, periventricular leukomalacia, bronchopulmonary dysplasia, necrotizing enterocolitis or retinopathy of prematurity requiring laser therapy) before the neonate was discharged from the hospital in the sildenafil-exposed group compared to placebo (Relative risk, 1.11; 95% CI, 0.88-1.40; P = .38).

(See DPMH review by Wenjie Sun, MD, October 5, 2020. DARRTS Reference ID 4680974, for a detailed review of the Dutch STRIDER results.)

One new reference was located in the search.

- Using data from the Dutch STRIDER Trial, investigators analyzed cerebral and renal regional tissues oxygen saturation (rSO2) within the first 72 hours after birth. Sildenafil exposed infants (n=5) showed lower renal rSO2 than placebo-exposed infants (n=6) on days 1 and 2. At 69-72 hours the sildenafil group showed higher renal rSO2 than the placebo group. Cerebral rSO2 levels were not different between treatment groups (n=14, both groups). The authors report that these data suggest that prenatal sildenafil alters renal, but not cerebral oxygenation in neonates with fetal growth retardation and postulate that these observed changes could reflect a vasoconstrictive rebound from sildenafil.[16]

[12] DPMH review of Sildenafil TheRapy in Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER) trial results and possible labeling change for subsection 8.1, Wenjie Sun, MD, October 5, 2020. DARRTS Reference ID 4680974
[13] [13] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 2/11/2021
[14] DPMH review of REVATIO, NDA 21845, Catherine Roca, M.D., Medical Officer, September 22, 2017. DARRTS ID #: 4157089
[15] Pels A, et al., Maternal sildenafil vs placebo in pregnant women with severe early-onset fetal growth restriction: a randomized clinical trial. *JAMA Netw Open* 2020;3(6):e205323.
[16] Terstappen F, et al. Prenatal use of sildenafil in fetal growth restriction and its effect on neonatal tissue oxygenation: a retrospective analysis of hemodynamic data from participants of the Dutch STRIDER trial. *Front Pediatr*. 2020;8:595693.

Reviewer comment:
The meta-analysis of the STRIDER trial data has been delayed and, according to Principal Investigator, will not be published before the second half of 2021.[17]

Review of Pharmacovigilance Database/Clinical Trials Data
The bioavailability/bioequivalence study conducted to support this NDA contained only male participants. There were no cases of pregnancy that occurred during the study.

Reviewer Comment:
The Sponsor concludes that there is no new information to include in labeling. The previous DPMH review of sildenafil indicated a potential labeling change based on publication of a meta-analysis of the Sildenafil TheRapy in Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER). The search of the literature found one new paper indicating possible vasoconstrictive rebound in neonates with fetal growth restriction exposed to sildenafil during development. The sample size of this study is small. Data from the STRIDER meta-analysis is not yet available.[18]

LACTATION
Nonclinical Experience
The reader is referred to the Lactation section of the relied upon drug labeling and to the Nonclinical review by Xi Yang, PhD and Jean Wu, PhD.

Applicant's Review of Literature
The applicant performed a search of the published literature from September 1, 2017 through January 2021 using the PubMed database and the search terms, "sildenafil," and "lactation."

No new references were found.

DPMH Review of Literature:
DPMH conducted an updated search of the literature from the time of the DPMH PLLR labeling review[19] (September 22, 2017) to present using *Medications in Mother's Milk,*[20] the Drugs and Lactation Database (LactMed),[21] Micromedex,**Error! Bookmark not defined.** and of the published literature in PubMed and Embase using the search terms "sildenafil and lactation," and "sildenafil and breast-feeding."

[17] Email communication with Dr. Ganzevoort, March 5, 2021.
[18] DPMH review of Sildenafil TheRapy in Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER) trial results and possible labeling change for subsection 8.1, Wenjie Sun, MD, October 5, 2020. DARRTS Reference ID 4680974
[19] DPMH review of REVATIO, NDA 21845, Catherine Roca, M.D., Medical Officer, September 22, 2017. DARRTS ID #: 4157089
[20] Hale's Medications and Mother's Milk. https://www.halesmeds.com/ accessed 2/11/2021
[21] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. 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 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 and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Hale's[22] rates sildenafil as "L3-No Data- Probably Compatible."

LactMed[23] reports "sildenafil and its metabolite are poorly excreted into breastmilk. Amounts ingested by the infant are small and would not be expected to cause any adverse effects in breastfed infants." LactMed also states:

> "*Maternal Levels.* A breastfeeding woman receiving sildenafil 20 mg for pulmonary hypertension. Breastmilk samples were taken 8 hours after a dose, followed by another dose 11 hours after the first. Then further milk samples were obtained about 3.5 and 6 hours after the second dose. The highest sildenafil and desmethylsildenafil milk levels of 4.49 mcg/L and 1.82 mcg/L, respectively, were in the second sample. Concentrations of sildenafil at the first and last samples were 1.64 and 1.67 mcg/L. Concentrations of desmethylsildenafil at the first and last sampling times were 1.18 and 1.73 mcg/L.
>
> *Infant Levels.* Relevant published information was not found as of the revision date.
>
> *Effects in Breastfed Infants:* A 23-year-old woman with congenital heart disease and pulmonary hypertension was treated during pregnancy with sildenafil and bosentan in unspecified dosages. These drugs and warfarin were continued postpartum. Her infant was delivered at 30 weeks by cesarean section and weighed 1.41 kg at birth. She nursed the infant in the neonatal intensive care unit for 11 weeks "with good outcome" according to the authors, but the infant died 26 weeks after birth from a respiratory syncytial virus infection.[24]
>
> *Effects on Lactation and Breastmilk*:
> Relevant published information was not found as of the revision date."

The DPMH review of the published literature did not yield any additional references.

<u>Review of Pharmacovigilance Database/Clinical Trial Data</u>
The bioavailability/bioequivalence study conducted to support this NDA contained only male participants; therefore there were no cases related to lactation that occurred during the study.

Reviewer Comment:
The Sponsor concludes that there is no information to inform a labeling change. This reviewer agrees; no new information on sildenafil and lactation was located since the last DPMH labeling review of REVATIO.

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[22] Hale's Medications and Mother's Milk. https://www.halesmeds.com/ accessed 2/11/2021
[23] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. 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 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 and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[24] Molelekwa V et al. Eisenmenger's syndrome in a 27 week pregnancy- management with bosentan and sildenafil. *Ir Med J*. 2005. 98:87-8.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

There was no impairment of fertility in male or female rats given up to 60 mg sildenafil/kg/day, a dose producing a total systemic exposure (AUC) to unbound sildenafil and its major metabolite of 19 and 38 times for males and females, respectively, the human exposure at the relative human dose of 20 mg three times a day. For further details, the reader is directed to the Nonclinical Review by Xi Yang, PhD and Jean Wu, PhD.

Applicant's Review of Literature

The applicant performed a search of the published literature from September 1, 2017 through January 2021 using the PubMed database and the search terms, "sildenafil," and "reproduction," "sperm, " "semen" and "testosterone."

The following publications were located:

- A systematic review of the literature of embryo transfer and therapeutic options in infertile patients with a thin endometrium. This review included three randomized clinical trials of sildenafil to increase endometrial thickness. Results were conflicting, with only one study indicating improved endometrial thickness.[25]
- A systematic review and meta-analysis on the use of sildenafil for the treatment of thin endometrium. This meta-analysis included nine studies (1452 patients). Overall, this meta-analysis concluded that women with a thin endometrium had increased thickness with sildenafil treatment compared to placebo (weighted mean difference 1.22, 95% CI 1.07-1.38) and higher clinical pregnancy rate (risk ratio 1.45, 95% CI 1.11-1.89).[26]
- No papers were located that indicated an adverse effect on female or male fertility.

DPMH Review of Literature:

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "sildenafil and fertility," "sildenafil and contraception," "sildenafil and oral contraceptives," and "sildenafil and infertility."

There were no articles found in the published literature related to adverse effects of sildenafil on hormonal contraception.

Sildenafil is indicated for the treatment of erectile dysfunction and can improve sexual function in men with this disorder.[27] Some,[28,29] but not all,[30] studies report that sildenafil may also

[25] Ranisavljevic N, et al. Embryo transfer strategy and therapeutic options in infertile patients with thin endometrium: a systematic review. *J Assist Reproduct Genetics*. 2019;36:2217-2231

[26] Li X, et al. Effect of sildenafil citrate on treatment of infertility in women with a thin endometrium: a systemic review and meta-analysis. *J Int Med Res*. 2020;48:1-14.

[27] VIAGRA (sildenafil citrate) package insert, Drugs@FDA.gov

[28] Pomara G. et al. Alterations in sperm motility after acute oral administration of sildenafil or tadalafil in young, infertile men. *Fertil Steril*. 2007. 88(4):860-5.

[29] Mostafa T. In vitro sildenafil use as a sperm motility stimulant. Fertil Steril. 2007. 88(4):994-6.

[30] Glenn DR, et al. Sildenafil citrate improves sperm motility but causes a premature acrosome reaction in vitro. *Fertil Steril*. 2007. 87(5):1064-70.

improve sperm motility. There also are reports in the literature of the use of sildenafil for female infertility related to thin endometrium.[31,32]

Review of Pharmacovigilance Database/Clinical Trials

The bioavailability/bioequivalence study conducted to support this NDA contained only male participants. There were no cases of male infertility during the study.

Reviewer Comment:
No data indicating an adverse effect on human fertility or interactions with hormonal contraception were found.

DISCUSSION AND CONCLUSIONS

Pregnancy

In the most recent review of sildenafil and the data from the Dutch STRIDER trial, it was unclear if the observed increase in neonatal pulmonary hypertension was due to sildenafil exposure. Recommendations for labeling at that time were to reevaluate after a meta-analysis of pooled data from the Dutch STRIDER trial is conducted. However, the reviewer recommended updating the language in 8.1 Pregnancy Risk Summary. The Risk Summary will be updated to, "Published data from randomized controlled trials, case-controlled trials, and case series do not report a consistent pattern with oral use of sildenafil in pregnancy and major birth defects, miscarriage or other adverse maternal or fetal outcomes."

Lactation

Published data from a case report describe the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant or on milk production. Labeling will include the Risk Summary and the following statement, "The devlopmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LIQREV and any potential adverse effecs on the breastfed infant from LIQREV or the underlying maternal condition."

Females and Males of Reproductive Potential

Nonclinical data do not indicate an adverse effect on fertility. A search of the published literature does not indicate an adverse effect on male or female fertility or an adverse effect on hormonal contraception. Data do not generally indicate an increase in congenital malformation or pregnancy complications. Subsection 8.3 does not need to be included in labeling. Animal data may remain in Section 13.

LABELING RECOMMENDATIONS

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

DPMH Proposed Pregnancy and Lactation Labeling

[31] Zinger M, Liu JH, Thomas MA. Successful use of vaginal sildenafil in two infertility patients with Asherman's syndrome. *J Womens Health*. 2006. 15(4):442-4.
[32] Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. *Fertil Steril*. 2002. 78(5):1073-6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published data from randomized controlled trials, case-controlled trials, and case series do not report a (b) (4) with (b) (4) sildenafil in pregnancy and major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus from untreated pulmonary artery hypertension *(see Clinical Considerations)*. Animal reproduction studies conducted with sildenafil showed no evidence of embryo-fetal toxicity or teratogenicity at doses up to 32- and 65-times the recommended human dose (RHD) of 20 mg three times a day in rats and rabbits, respectively *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population 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 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women with untreated pulmonary artery hypertension are at risk for heart failure, stroke, preterm delivery, and maternal and fetal death.

Data

Animal Data

No evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed in pregnant rats or rabbits dosed with sildenafil 200 mg/kg/day during organogenesis, a level that is, on a mg/m^2 basis, 32- and 65-times, respectively, the recommended human dose (RHD) of 20 mg three times a day. In a rat pre- and postnatal development study, the no-observed-adverse-effect dose was 30 mg/kg/day (equivalent to 5-times the RHD on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Limited published data from a case report describes the presence of sildenafil and its active metabolite in human milk. There is insufficient information about the effects of sildenafil on the breastfed infant and no information on the effects of sildenafil on milk production. Limited clinical data during lactation preclude a clear determination of the risk of REVATIO to an infant during lactation. (b) (4)

(b) (4)

Appendix A: Summary of Studies of Sildenafil Citrate in Pregnancy prior to 2017[33]

Table 1. Summary of included studies

First author, year [Ref.]	Publication	Country	Indication	Cohort size	Maternal age, years	SC regimen	SC duration, days	GA at SC start, weeks
Trapani, 2016 [24]	RCT	Brazil	PET	50	25.3±5.4	50 mg PO 8-hourly	14.4[b]	29.1±2.1
Trapani, 2016 [29]	RCT	Brazil	FGR	12	23.6±6.2	50 mg PO[a]	NR	28.5±2.1
Dastjerdi, 2012 [12]	RCT	Iran	FGR	14	25.6±1.5	50 mg PO once	1	35±2
Samangaya, 2009 [23]	RCT	UK	PET	17	28 (24–34)	20–80 mg PO 8-hourly	4 [1–15]	31.4 (26.6–32.5)
El-Far, 2014 [25]	Non-RCT	Egypt	URSM	40	*	25 mg PV 6–8-hourly	13 or 24	<13
von Dadelszen, 2011 [26]	Case controlled	Canada	FGR	10	34 (25–40)	25 mg PO 8-hourly	31.5 (9.5–81)	22.4
Subbaiah, 2013 [16]	Cohort	India	PH	4	NR	20 mg PO 8-hourly	NR	NR
Duarte, 2013 [17]	Case series	USA	PH	4	23.5 [19–34]	20–50 mg PO	66.5 [49–196]	25.5 [6–29]
Kiely, 2010 [18]	Case series	UK	PH	3	23 [21–38]	25 mg PO 8-hourly	7 [7–238]	31 [0–33]
Goland, 2010 [19]	Case series	USA	PH	2	21; 30	25–50 mg PO 8-hourly	7; 31	36; 32
El-Far, 2009 [13]	Case series	Egypt	URSM	4	27 [22–30]	25 mg PV 6-hourly	23 [20–24]	9 [6–11]
Panda, 2014 [27]	Case report	India	FGR	1	32	50 mg PO 8–12-hourly	21	26.6
Lin, 2012 [28]	Case report	Taiwan	FGR	1	30	25 mg PO 8-hourly	48	26
Ng, 2012 [20]	Case report	Singapore	PH	1	30	25 mg PO 8-hourly	1	35
Molelekwa, 2005 [21]	Case report	Ireland	PH	1	23	NR	14	28
Lacassie, 2004 [22]	Case report	Chile	PH	1	22	50–150 mg PO daily	98	0[c]

Data are mean ± standard deviation, median (interquartile range), or median [range]. * Maternal age (median [range]) reported for each SC cohort: 27 years [19–35] and 26.5 years [20–33]. [a] Frequency not reported. [b] Average duration of SC dosing. [c] SC 50 mg PO daily from conception until 9 weeks and then recommenced at 31 weeks until delivery at 36 weeks. RCT, randomised controlled trial; Non-RCT, non-randomised controlled trial; SC, sildenafil citrate; PET, preeclampsia; FGR, fetal growth restriction; URSM, unexplained recurrent spontaneous miscarriage; PH, pulmonary hypertension; NR, not reported; PO, per oral; PV, per vaginal; GA, gestational age.

[33] Dunn L, et al. Sildenafil in Pregnancy: A systematic review of maternal tolerance and obstetric and perinatal outcomes. Fetal Diagn Ther. 2017;41:81-88.

Table 3. Obstetric and perinatal outcomes following sildenafil citrate use in pregnancy

First author, year [Ref.]	Indication	Caesarean section	Vaginal delivery	Postpartum haemorrhage	Apgar <7 at 5 min	Cord arterial pH <7.1	Nursery admission	Congenital anomaly	Stillbirth	Neonatal death
Overall rate (%)	–	55/66 (83.3)	11/66 (16.7)	3/76 (3.9)	4/56 (7.1)	0/17 (0)	35/52 (67.3)	0/35 (0)	3/69 (4.3)	5/129 (3.9)
Trapani, 2016 [24]	PET	42/50	8/50	1/50	4/50	NR	33/50	[d]	NR	2/50
Trapani, 2016 [29]	FGR	NR	NR	NR	NR	NR	NR	[d]	NR	0/12
Dastjerdi, 2012 [12]	FGR	NR	NR	NR	NR	NR	NR	[d]	NR	NR
Samangaya, 2009 [23]	PET	NR	NR	1/17	NR	0/17	NR	NR	0/17	1/17
El-Far, 2014 [25]	URSM	NR	NR	NR	NR	NR	NR	0/24	0/24	0/24
von Dadelszen, 2011 [26]	FGR	NR	NR	NR	NR	NR	NR	[b]	3/10	2/10
Subbaiah, 2013 [16]	PH	1/2	1/2	0/4	NR	NR	NR	0/4	0/4	0/4
Duarte, 2013 [17]	PH	4/4	0/4	NR	NR	NR	NR	NR	0/4	0/4
Kiely, 2010 [18]	PH	2/3	1/3	NR	0/2	NR	NR	0/3	0/3	0/3
Goland, 2010 [19]	PH	2/2	0/2	0/2[a]	0/1	NR	NR	0/1	0/2	0/2
El-Far, 2009 [13]	URSM	NR	NR	NR	NR	NR	NR	NR	NR	NR
Panda, 2014 [27]	FGR	1/1	0/1	NR	NR	NR	1/1	0/1	0/1	0/1
Lin, 2012 [28]	FGR	1/1	0/1	NR	0/1	NR	NR	NR	0/1	0/1
Ng, 2012 [20]	PH	0/1	1/1	0/1	0/1[c]	NR	NR	0/1	0/1	NR
Molelekwa, 2005 [21]	PH	1/1	0/1	1/1	NR	NR	1/1	0/1	0/1	0/1
Lacassie, 2004 [22]	PH	1/1	0/1	0/1[b]	0/1	NR	NR	NR	0/1	NR

PET, preeclampsia; FGR, fetal growth restriction; URSM, unexplained recurrent spontaneous miscarriage; PH, pulmonary hypertension; NR, not reported. [a] "Uneventful" delivery and "stable" postpartum. [b] "Uneventful" delivery. [c] "Baby was healthy with an Apgar score of 9" (time not specified). [d] Exclusion criteria in these studies.

Appendix B: Major studies of sildenafil use in pregnancy[34]

[34] DPMH review of Sildenafil TheRapy in Dismal prognosis Early-onset intrauterine growth Restriction (STRIDER) trial results and possible labeling change for subsection 8.1, Wenjie Sun, MD, October 5, 2020. DARRTS Reference ID 4680974

Publication	Type	N (exposed)/drug/disease	Timing	Exposure	Outcome	Comments (Strengths (S) /Limits (L))
Pels A, et al.[29] (2020) Netherland	RCT	108 exposed; sildenafil 25 mg po TID used until 32 weeks or delivery	starting 20-30 weeks until 32 weeks	216 IUGR pregnancies (defined by fetal abdominal circumference <3% or EFW <5%) randomized to 108 exposed and 108 placebos followed. -primary outcome was fetal mortality and morbidity	-Neonatal death was present in 24.7% (21/85) in the sildenafil group vs 14.1% (11/78) in the placebo group (RR 1.65; 95% CI, 0.9-3.39; P = 0.1). 4 neonatal deaths were attributable to PH in 4 infants. -PH occurred 16 neonates (18.8%) in sildenafil group vs 4 (5.1%) in the placebo group (RR 3.67; 95% CI, 1.28-10.51; P=0.008). The trial was stopped. 2 types of PPHN and later-onset PH associated with either sepsis or BPD were present. -No difference in composite primary outcome of perinatal mortality or major neonatal morbidity until hospital discharged (60.2% exposed vs 54.2% placebo, RR 1.11; 95% CI, 0.88-1.40; P=0.38) -No difference in proportion of mothers experiencing preeclampsia or HELLP; No difference in maternal UA or fetal UA or MCA doppler. -No difference in birth weight	S- randomized, controlled, double-blinded; L- trial was stopped before planned sample size due to safety; No long-term data
Sharp A, et al.[30] (2018) UK	RCT	70 exposed sildenafil 25 mg po TID used until 32 weeks or delivery	starting 22^{+0}-29^{+6} weeks until 32 weeks	135 IUGR pregnancies (defined by fetal abdominal circumference <10% or EFW <10% and AEDF or REDF) randomized to 70 exposed and 65 placebos followed. -primary outcome was the time from randomization to delivery	-No difference in the median randomization to delivery interval (17 days exposed vs 18 days placebo); livebirths (RR 1·06, 95% CI 0·84 to 1·33; p=0·62), fetal deaths (0·89, 0·54 to 1·45; p=0·64), neonatal deaths (1·33, 0·54 to 3·28; p=0·53), and birthweight (–14 g,–100 to 126; p=0·81). -There were 10 neonatal death in sildenafil group vs 7 in placebo. Of these, there were 1 case of PH in each group.[31] -No differences were found for any other secondary outcomes.	S- randomized, controlled, double-blinded; L-looser definition of IUGR; no long-term data

[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] Sharp A, et al. Maternal sildenafil for severe fetal growth restriction (STRIDER): a multicentered, randomized, placebo-controlled, double-blind trial. Lancet Child Adolesc Health 2018; 2:93-102.

[31] Sharp A, et al. Mortality in the UK STRIDER trial of sildenafil therapy for the treatment of severe early-onset fetal growth restriction. Lacet. 2019(3):e2-3. http://dx.doi.org/10.1016/S2352-4642(19)30020-3

				-secondary outcome included live birth, fetal and neonatal death, birthweight, neonatal morbidity; use of surfactant, ventilator dependency, admission to NICU, time to newborn discharge, and maternal side-effects.	-Eight serious adverse events were reported during the course of the study (six in the placebo group and two in the sildenafil group); none of these were attributed to sildenafil. -Ductus venosus a-wave deteriorated over time in more women treated with sildenafil than placebo (18 out of 19 deteriorated were randomly assigned before 26 weeks' gestation), no other changes between the groups in uterine artery, fetal UA and MCA dopplers. -angiogenic biomarker did not change over time or because of sildenafil (VEGF concentration were found to be below the lowest assay standard in all cases).	
Groom KM, et al.[32] (2019) Australia/New Zealand	RCT	63 exposed sildenafil 25 mg po TID used until 32 weeks or delivery	starting 22^{+0}-29^{+6} weeks until 32 weeks	122 IUGR pregnancies (defined by fetal abdominal circumference <3% at 22-27+6 weeks and EFW <700g at 28-29^{+6} weeks of gestation) randomized to 63 exposed and 59 placebos followed. -primary outcome was the proportion of pregnancies with an increase in fetal growth velocity. Secondary outcomes included live birth, survival to hospital discharge free of major neonatal morbidity and pre-eclampsia.	-No difference in proportion of pregnancies with an increase in fetal growth velocity; 32/61 (52.5%) treated vs 39/57 (68.4%) placebo-treated [adjusted odds ratio (OR) 0.49, 95% CI 0.23–1.05] and had no effect on abdominal circumference Z-scores (P = 0.61). -Sildenafil use was associated with a lower mean uterine artery pulsatility index after 48 hours of treatment (1.56 versus 1.81; P = 0.02). -The live birth rate was 56/63 (88.9%) for sildenafil-treated and 47/59 (79.7%) for placebo-treated (adjusted OR 2.50, 95% CI 0.80–7.79); survival to hospital discharge free of major neonatal morbidity was 42/63 (66.7%) for sildenafil-treated and 33/59 (55.9%) for placebo-treated (adjusted OR 1.93, 95% CI 0.84–4.45); and new-onset pre-eclampsia was 9/51 (17.7%) for sildenafil-treated and 14/55 (25.5%) for placebo-treated (OR 0.67, 95% CI 0.26–1.75). -Sildenafil did not affect maternal blood pressure after treatment but lowered mean uterine pulsatility index, but this effect was not sustained with time. No effect on UA, MCA or ductus venosus PI at 48 hours or more time.	S- randomized, controlled, triple-blinded; >90% compliance by 93.4% patients L-results based on ultrasound finding; sample size
da Silva Ferreira RD, et	Systematic review and	598 pregnant women in 7 clinical trial	starting between 24-30 weeks	A literature search of RCT using sildenafil vs placebo included 7 trial with 598 pregnant women (139 had pre-eclampsia, 275 had	-Fetal birthweight was analyzed in 5 trials, 508 patients, 255 in sildenafil group and 253 in placebo group, an increase of 75.55grams [49.27 to 101.83 grams] in fetal weight at birth was observed. However, as a high heterogeneity between the studies	S-larger number L-heterogenous population (no appropriate randomization and blind allocation in 1/3 of the

[32] Groom KM, et al. ATRIDER NZAus: a multicentre randomised controlled trial of sildenafil therapy in early-onset fetal growth restriction. 2019 Jul;126(8):997-1006. doi: 10.1111/1471-0528.15658

al.[33] (2019) Brazil	meta-analysis	sildenafil 50mg-150mg daily		intrauterine growth restriction, and 184 had oligohydramnios); outcomes were fetal weight at delivery, indication of the resolution of pregnancy, gestational age at birth, UA pulsatility index, neonatal mortality and medication tolerance.	was identified. This resulted in a significant increase of 222.58 grams [27.75 to 417.41] was observed in the fetal weight at birth of patients taking sildenafil. -There is no difference in the groups regarding the UA PI, indication of gestational resolution, neonatal death, maternal headaches.	trials, loss greater than 20% of the initial sample occurred in 2 studies) with variable doses used.
Maged M, et al.[34] (2018) Egypt	Prospective controlled	25 exposed Sildenafil 20mg TID until delivery	starting 24-32 weeks until delivery	50 women (25 exposed vs 25 not exposed) with IUGR (EFW <10% or AC <10% with abnormal UA Doppler indices).	-UA doppler indices after 4 weeks of treatment showed significant decreased in S/D ratio in treated group compared to control. -livebirth was 24/25 in exposed vs 22/25 control. -mean GA at delivery was 35.3 weeks in exposed vs 34.8 weeks in control. -birthweight was 2066.8g in exposed vs 1732.8g in control. -admission to NICU was 7 in exposed vs 15 in control.	L- not randomized
Shehata NAA, et al.[35] (2020) Egypt	RCT	23 exposed Sildenafil 20mg TID until undisclosed time and zinc 25mg daily and fish oil 150mg BID	starting 24-34 weeks	46 women (25 exposed vs 23 control) with IUGR (AC <5% with estimated intact survival of <50%).	-UA and MCA Doppler indices showed significant difference between groups after intake of sildenafil. Umbilical artery pulsatility index decreased significantly (p value ¼ .001) while middle cerebral artery pulsatility index increased significantly in intervention group (p value0.001. -abdominal circumference growth velocity improved after two weeks of sildenafil intake (p value ¼ .001).	L-small sample size, neonatal morbidity and mortality not evaluated.

RCT: randomized controlled trial; IUGR: intrauterine growth restriction EFW: estimated fetal weight; PH: pulmonary hypertension; PPHN: persistent PH; PAH: pulmonary arterial hypertension (PH group1); HELLP: hemolysis, elevated liver enzyme, and low platelets syndrome; UA: umbilical artery, MCA: middle cerebral artery; AEDF: absent end-diastolic flow of the fetal umbilical artery on doppler velocimetry; REDF: reversed end-diastolic flow of the fetal umbilical artery on doppler velocimetry; PI- pulsatility index; HC, head circumference; AC: abdominal circumference; GA: gestational age; BPD: bronchopulmonary dysplasia

[33] da Silva Ferreira R.D., Negrini R., Bernardo W.M., Simões R., Piato S. The effects of sildenafil in maternal and fetal outcomes in pregnancy: A systematic review and meta-analysis. PLoS ONE 2019 14:7 https://doi.org/10.1371/journal.pone.0219732

[34] Maged M, et al. Use of sildenafil citrate in cases of intrauterine growth restriction (IUGR); a prospective trial. Taiwanese Journal of Obstetrics & Gynecology 2018; 57: 483-486.

[35] Shehata N, et al. Addition of sildenafil citrate for treatment of severe intrauterine growth restriction: a double-blind randomized placebo-controlled trial. The Journal of Maternal-Fetal & Neonatal Medicine 2020; 33(10): 1631–1637

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