

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216203Orig1s000

OTHER REVIEW(S)



DIVISION OF CARDIOLOGY AND NEPHROLOGY

Regulatory Project Manager Review

NDA: 216203
Drug: INPEFA (sotagliflozin) tablets, for oral use
Strengths: 200 & 400 mg
Class: SGLT2 inhibitor
Applicant: Lexicon Pharmaceuticals, Inc.

Proposed Indication: Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure.

Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.

Final Approved Indication: INPEFA is indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:

- heart failure or
- type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors

FDA Received: May 27, 2022
Approval date: May 26, 2023
PDUFA date: May 27, 2023

❖ REVIEW TEAM

Office of Cardiology, Hematology, Endocrinology, and Nephrology

- Lisa Yanoff, MD Deputy Director, Signatory

Office of Cardiology, Hematology, Endocrinology, and Nephrology, Division of Cardiology and Nephrology

- Norman Stockbridge Director
- Aliza Thompson Deputy Director/Nephrology Team Leader
- Mary Ross Southworth Deputy Director for Safety

- | | |
|----------------------|--------------------------------|
| • Michael Monteleone | Associate Director of Labeling |
| • Charu Gandotra | Cross Disciplinary Team Leader |
| • Jordan Pomeroy | Clinical Reviewer – Efficacy |
| • Christine Garnett | Safety Team Leader |
| • Yanyan Ji | Safety Reviewer |
| • Tejas Patel | Safety Reviewer |

Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

- | | |
|----------------|-----------------------------------|
| • Edward Fromm | Chief, Project Management Staff |
| • Bridget Kane | Regulatory Health Project Manager |

Office of Pharmaceutical Quality

Office of New Drug Products

- | | |
|---------------------------|---|
| • Ted Carver | Application Technical Lead |
| • Joseph Leginus | Drug Substance Primary |
| • Sithamalli Chandramouli | Drug Substance Secondary |
| • Ali Mohamadi | Drug Product/Labeling |
| • Zhuojun Zhao | Biopharmaceutics Primary |
| • Haritha Mandula | Biopharmaceutics Secondary |
| • Grafton Adams | Sr. Regulatory Business Project Manager |

Office of Pharmaceutical Manufacturing Assessment (Process & Facilities)

- | | |
|-------------------|-------------------------|
| • Alex Gontcharov | Manufacturing Primary |
| • Feiyan Jin | Manufacturing Secondary |

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology

- | | |
|-----------------|--------------------------|
| • Todd Bourcier | Director |
| • Xuan Chi | Non-Clinical Team Leader |
| • Baichun Yang | Non-Clinical Reviewer |

Office of Clinical Pharmacology, Division of Cardiometabolic & Endocrine Pharmacology (DCEP)

- | | |
|------------------|-----------------------------------|
| • Doanh Tran | Deputy Division Director |
| • Snehal Samant | Clinical Pharmacology Team Leader |
| • Mohamad Nounou | Clinical Pharmacology Reviewer |

Office of Biostatistics, Division of Biometrics II

- | | |
|-----------------|----------------------|
| • Mark Rothmann | Director |
| • Jialu Zhang | Team Leader |
| • Ququan Liu | Statistical Reviewer |

Office of Surveillance and Epidemiology, Office of Medication Error Prevention and Risk Management

Division of Medication Error Prevention and Analysis 2

- Hina Mehta Team Leader
- Janine Stewart Safety Evaluator
- Monique Killen Sr. Regulatory Health Project Manager

Division of Risk Management

- Laura Zendel Associate Director for REMS
- Yasmeen Abou-Sayed Team Leader
- Courtney Cunningham Reviewer

Consult Reviewers (Labeling)

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, Division of Pediatrics and Maternal Health (DPMH)

- Lynne Yao Director
- Miriam Dinatale Team Leader
- Wenjie Sun Reviewer

Office of Medical Policy

Office of Medical Policy Initiatives, Division of Medical Policy Programs, Patient Labeling Team

- LaShawn Griffiths Associate Director for Patient Labeling
- Ruth Mayrosh Senior Patient Labeling Reviewer
- Jessica Chung Patient Labeling Reviewer

Office of Prescription Drug Promotion

- Susannah O'Donnell Team Leader
- Meena Savani Regulatory Review Officer

❖ BACKGROUND

Sotagliflozin, a sodium-glucose co-transporter type 1 (SGLT1) and sodium-glucose co-transporter type 2 (SGLT2) inhibitor, was originally developed by Lexicon Pharmaceuticals under IND 102191 (DDLO) for type 1 diabetes mellitus (T1DM) (b) (4)

An NDA was submitted for sotagliflozin for the treatment of T1DM but the Agency issued a Complete Response Letter on March 22, 2019 because there was an unfavorable benefit/risk assessment due to diabetic ketoacidosis in sotagliflozin vs. placebo. Thus, sotagliflozin had yet to be approved for any indications.

In June 2017, Lexicon met with the Division of Cardiology and Nephrology, under PIND 135095, to discuss the development of sotagliflozin for the heart failure (HF). The Sponsor proposed to conduct the SOLOIST study, a phase 3, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of sotagliflozin to reduce the risk of cardiovascular (CV) death, hospitalization for heart failure (HHF) and urgent heart failure

visit (UHFV) in patients with HF and T2DM. The Sponsor submitted a new IND on January 31, 2018, and the Division deemed the SOLOIST study safe to proceed on March 26, 2018. The SCORED study, conducted under IND 102191, was a phase 3, placebo-controlled, double-blind trial designed to evaluate the efficacy and safety of sotagliflozin to reduce the risk of CV death, HHF, and UHFV in patients with T2DM, chronic kidney disease with estimated glomerular filtration rate (eGFR) ≥ 25 to ≤ 60 mL/min/1.73 m², and either a major CV risk factor or age ≥ 55 years with at least 2 minor CV risk factors. The INDs were transferred to Sanofi from November 2015 to July 2019. These studies were stopped early (March 2020) due to “business reasons and study operational complications associated with COVID-19”. Lexicon resumed ownership of the sotagliflozin INDs in 2020. Prior to data lock (August 2020), the Sponsor modified the Statistical Analysis Plan to change the primary endpoint for both studies to: the composite of CV death, HHF, and UHFV. At a Type C Meeting in January 2021, the Division agreed that the results from the SOLOIST and SCORED studies could support an NDA.

Both studies reached statistical significance on the primary endpoint. A total of 10,584 patients were randomized in SCORED with the first patient enrolled in December 2017; 1,222 patients were randomized in SOLOIST with the first patient enrolled in June 2018. The last patient last visit was conducted in early July 2020.

The Applicant submitted NDA 216203 for sotagliflozin oral tablets (200 and 400 mg) on December 30, 2021. (b) (4)

The Division notified the Applicant of its concerns and the Applicant withdrew the application on February 28, 2022 (Refer to Memo to File dated March 1, 2022).

Subsequently, the Applicant requested a Type A Meeting to discuss their proposed plan to recertify the data and resubmit the application. The Division sent Preliminary Comments on April 25, 2022, and the Applicant deemed the responses sufficient.

The Applicant resubmitted NDA 216203 on May 27, 2022 and requested priority review. The filing meeting was held on July 7, 2022. The Division filed the NDA on July 26, 2022 as a Standard Review. Sotagliflozin is considered a New Molecular Entity and was reviewed under “the Program”. The Division consulted the Division of Pediatrics and Maternal Health (PLLR), the Office of Prescription Drug Promotion, the Patient Labeling Team to review the submitted labeling.

There were no major review issues identified during the review cycle. The review team determined there was no need for a REMS (Refer to DRM Review: Cunningham, May 25, 2023) or Postmarketing Requirements or Commitments. See the Discipline Review section for conclusions reached during the review.

REGULATORY TIMELINE

Stamp Date (original submission):	December 30, 2021
NDA Withdrawal	February 28, 2022
Type A Meeting (Prelim. Comments):	April 25, 2022
Resubmission:	May 27, 2022
Filing Meeting	July 7, 2022
NDA Filed:	July 26, 2022
74-day Letter:	August 8, 2022
Site Selection Meeting:	June 29, 2022 (no inspections)
Team Meeting:	September 7, 2022
Midcycle Prep:	October 6, 2022
Mid-cycle Meeting:	October 27, 2022
Midcycle Comm. with Applicant:	November 7, 2022
Labeling Meeting #1	November 14, 2022
Labeling Meeting #2	November 28, 2022
Labeling Meeting #3	December 14, 2022
Labeling Meeting #4:	January 11, 2023
Team Meeting (late-cycle prep):	January 30, 2023
Labeling Meeting:	February 14, 2023
Late-cycle Meeting w/Applicant:	February 27, 2023
PeRC Meeting:	March 28, 2023

❖ USER FEE

The user fee for this application was paid in full on May 13, 2022 (User fee ID #3018168).

❖ PEDIATRIC REVIEW COMMITTEE (PeRC)

This application triggered PREA (21 U.S.C. 355c) and the applicant requested a full waiver from pediatric assessments because necessary studies would be impossible or highly impracticable because the number of pediatric patients with heart failure or with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors is small, and there is no established/agreed upon bridging biomarker for SGLT2 inhibition for heart failure benefits. The application/request was reviewed by the PeRC on March 28, 2023. The Division and the PeRC agreed with the Applicant's request for full waiver of pediatric studies (PeRC Meeting Minutes - Covert, May 4, 2023).

❖ ADVISORY COMMITTEE (AC)

This application was not referred to an FDA AC because there were no controversial issues that would benefit from outside expertise/AC discussion.

❖ TRADE NAME

The Agency conditionally accepted the Applicant's preferred proprietary name, INPEFA, on April 27, 2023 (Topper, April 26, 2023).

❖ REVIEW STATUS

Sotagliflozin is a New Molecular Entity. This application was deemed a Standard Review under “the Program”.

❖ FACILITIES

Per the Integrated Quality Assessment, (Carver, January 27, 2023), the Office of Pharmaceutical Manufacturing Assessment deemed all listed facilities acceptable to perform their intended functions for commercial manufacture. Prior to taking action on this application, the facilities reviewer confirmed that the facilities remained in good standing (Email Gontcharov/Kane, May 18, 2023).

❖ INSPECTIONS

There were no site inspections for pivotal trials SOLOIST and SCORED. The Clinical and Statistical review teams did not observe any particular inequalities or areas of concern that would signal the need for inspection.

The Clinical Pharmacology Team requested clinical and analytical site inspections for Bioequivalence Study #BEQ14993. Per the Bioequivalence Establishment Inspection Report Review, dated October 5, 2022, an inspection of the clinical site was not needed because an inspection was conducted in 2021 for (b) (4) with No Action Indicated (b) (4) (). A Remote Regulatory Assessment (RRA) of the analytic portion of Study #BEQ14993 was conducted by the Office of Study Integrity and Surveillance (OSIS) and no objectionable conditions were observed. Therefore, the data from the referenced study was considered reliable (Sanyal, February 28, 2023).

❖ LABELING REVIEW

Labeling discussions began January 25, 2023 and final agreement on labeling was reached with the firm on May 26, 2023. For a summary of major labeling topics, refer to CDTL Memo (Gandotra, May 13, 2023).

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the review team members, organized by discipline. For full details, see referenced reviews in DARRTS.

CDTL Memorandum with DCN and OCHEN concurrence (May 13, 2023 – C. Gandotra, N. Stockbridge, L. Yanoff)

Recommendation: Approval

Dr. Gandotra summarized and agreed with the conclusions of the review team outlined below; Drs. Stockbridge and Yanoff concurred with this assessment.

Clinical & Biometrics Review (March 23, 2023 – J. Pomeroy/C. Gandotra, T. Patel/C. Garnett, Q. Liu/J. Zhang/M. Rothmann)

Recommended Action: Approval

The reviewers concluded that

- Data from SOLOIST and SCORED met the statutory requirement for substantial evidence of effectiveness and supported a favorable benefit-risk assessment of sotagliflozin “to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visits in adults with heart failure or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors.”
- Early termination of the trials for business decisions did not impact successful randomization, stratification or blinding and allowed for sufficient follow-up time to characterize the effect of sotagliflozin on the pre-specified primary composite endpoint.
- There were no meaningful imbalances in the incidence of deaths, serious treatment-emergent adverse events (TEAEs), and TEAEs leading to discontinuation between treatment groups in either study.
- The safety profile of sotagliflozin is generally consistent with other approved SGLT2i, except for diarrhea.
- T2DM should be considered an enrichment factor for HF in SOLOIST and SCORED and data from these studies demonstrated a preservation of benefit in adults with HF regardless of LVEF. Therefore, the reviewer’s recommended broadening the indication to *adults with heart failure* or type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors.

Clinical Pharmacology and Pharmacometrics Review (March 16, 2023 – M. Nounou, Y. Yuan, H. Zhu, S. Samant, and D. Tran)

Recommended Action: Approval

The reviewers concluded that data from the SOLOIST and SCORED trials support the proposed doses of 200 or 400 mg once daily. A bioequivalence study, #BEQ14993, supported bridging of the phase 3 trial dose of 400 mg (2 x 200 mg tablet) to the to-be-marketed 400 mg-tablet. A drug interaction for Lithium was added to Section 7 as a class labeling change.

Office of Product Quality Integrated Review (January 27, 2023 – Multiple reviewers)

Recommended Action: Approval

The reviewers concluded that the submitted data/assessments, specifications and controls are sufficient to adequately characterize and ensure the potency, purity, and quality of sotagliflozin tablets. All manufacturing facilities are deemed acceptable to perform their intended functions for commercial manufacturing. There were no facilities inspections during this review cycle. The facility recommendations are based off previous history. See full review located in DARRTS for a detailed assessment of each CMC aspect (Carver, January 27, 2023).

Non-Clinical Review

Recommended Action: Approval

Primary Review (October 28, 2022 – B. Yang/X. Chi)

The non-clinical data was previously reviewed under NDA 210934 and deemed supportive of approval (Brundage, November 28, 2018; Bourcier, February 22, 2022). Dr. Yang

concluded that the additional non-clinical data submitted for sotagliflozin supported approval of sotagliflozin.

Secondary Review (February 10, 2023 – X. Chi, T. Bourcier)

Drs. Chi and Bourcier agreed with Dr. Yang's conclusions.

Although the Applicant proposed that the established pharmacologic class (EPC) of sotagliflozin was SGLT1 and SGLT2, the reviewers concluded that the EPC of sotagliflozin is only SGLT2 because the submitted data/rationale do not support a discernible contribution of SGLT1 to the cardiac/heart failure benefit of sotagliflozin beyond that of SGLT2.

The reviewers also recommended that the risk summary and animal data sections for Section 8.1 disclose the renal pelvic dilatation and other renal changes in rats from the post-natal developmental and juvenile toxicology studies with sotagliflozin, which are considered relevant to fetal renal development during the second and third trimesters of pregnancy.

❖ CONSULT/LABELING REVIEWS

The following is a list of the consult/labeling reviews for sotagliflozin. See full reviews in DARRTS for a summary of labeling recommendations and conclusions.

- DPMH (PLLR Review): W. Sun, M. Dinatale, L. Yao – November 22, 2022
- DMEPA (PI, Med Guide, Carton/Container): J. Stewart, H. Meta – November 28, 2022
- OPDP (PI, Med Guide, Carton/Container): M. Savani – April 28, 2023
- PLT (PI, Med Guide): J. Chung, M. Savani, R. Mayrosh, L. Griffiths – May 3, 2023
- DMEPA (Carton/Container): J. Stewart, H. Mehta – May 19, 2023

❖ CONCLUSION

After considering the primary and consult reviews for NDA 216203, the Office of Cardiology, Hematology, Endocrinology, and Nephrology issued an approval letter signed by Dr. Lisa Yanoff, Deputy Office Director, on May 26, 2023.

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/s/

BRIDGET E KANE
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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: May 19, 2023
Requesting Office or Division: Division of Cardiology and Nephrology (DCN)
Application Type and Number: NDA 216203
Product Name and Strength: Inpefa ^a(sotagliflozin) tablets, 200 mg and 400 mg
Applicant/Sponsor Name: Lexicon Pharmaceuticals, Inc.
TTT ID #: 2022-2261-1
DMEPA 2 Safety Evaluator: Janine Stewart, PharmD
DMEPA 2 Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 20, 2023 for Inpefa. Division of Cardiology and Nephrology (DCN) requested that we review the revised container labels and carton labeling for Inpefa (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.^b

2 CONCLUSION

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

^a Labels and labeling submitted by the Applicant for NDA 216203 includes the proposed proprietary name, Inpefa, which was previously denied on January 28, 2022. Subsequently, the proprietary name, (b) (4) was found conditionally acceptable for NDA 216203 on September 7, 2022. Lexicon withdrew the conditionally acceptable name (b) (4) and resubmitted the proposed proprietary name, Inpefa, for review on March 1, 2023. DMEPA found proposed proprietary name, Inpefa, conditionally acceptable on April 26, 2023.

^b Stewart, J. Label and Labeling Review for (b) (4) (NDA 216203). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 NOV28. RCM No.: 2022-2261.

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/s/

JANINE A STEWART
05/19/2023 04:57:54 PM

HINA S MEHTA
05/19/2023 09:23:20 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: May 2, 2023

To: Bridget Kane, MS
Senior Regulatory Health 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)

Ruth Mayrosh, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Jessica Chung, PharmD, MS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Meena Savani, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TRADENAME (sotagliflozin)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 216203

Applicant: Lexicon Pharmaceuticals, Inc.

1 INTRODUCTION

On May 27, 2022, Lexicon Pharmaceuticals, Inc. resubmitted for the Agency's review an original New Drug Application (NDA) 216203 for TRADENAME (sotagliflozin) tablets after their application was voluntarily withdrawn on February 28, 2022. The proposed indications for TRADENAME (sotagliflozin) tablets are to:

- Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure.
- Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.

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 July 10, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (sotagliflozin) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (sotagliflozin) tablets MG received on May 27, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 20, 2023.
- Draft TRADENAME (sotagliflozin) tablets Prescribing Information (PI) received on May 27, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 20, 2023.

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 MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
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MEENA R SAVANI
05/03/2023 08:38:16 AM

RUTH I MAYROSH
05/03/2023 09:11:50 AM

LASHAWN M GRIFFITHS
05/03/2023 10:51:21 AM

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

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

Memorandum

Date: April 28, 2023

To: Bridget Kane, Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

Michael Monteleone, MS, RAC
Associate Director for Labeling, DCN

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Sotagliflozin tablets, for oral use

NDA: 216203

Background:

In response to DCN's consult request dated June 10, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for sotagliflozin.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 20, 2023, and our comments are provided below.

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

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on January 20, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

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/s/

MEENA R SAVANI
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MEMORANDUM

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

DATE: February 28, 2023

TO: Norman Stockbridge, MD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and
Nephrology (OCHEN)
Office of New Drugs (OND)

FROM: Sarmistha Sanyal, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: [REDACTED] (b) (4)
[REDACTED] (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA)¹ of the analytical portion of Study BEQ 14993 (NDA 216203, sotagliflozin), conducted at [REDACTED] (b) (4)

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited studies are reliable.

2. Reviewed Studies

NDA 216203

Study BEQ 14993

A bioequivalence study testing two formulations of sotagliflozin in healthy male and female subjects under fasted conditions.

Sample Analysis Period: 04/16/2019 – 07/16/2019

1. One set of tools for oversight of regulated products used during the pandemic has been remote regulatory assessments (RRAs). The term “RRA” describes a category of activities for which FDA may use different terminologies, but all are considered to be types of RRAs, including “remote record reviews” and “remote interactive evaluations.”

3. Scope of RRA

OSIS scientist Sarmistha Sanyal, PhD, reviewed the analytical portion of the above study conducted (b) (4) from (b) (4)

The RRA included an examination of records and processes for method validation, study sample analysis, analytical facility (including sample storage area and instruments), LC/MS software user permission and roles and study data management. The RRA also included interviews with the firm's management and staff.

4. RRA Observations

At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

Draft: SS 02/27/2023

Edit: SA 2/27/2023; JC 2/27/23

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ (b) (4)

OSIS File #: BE (b) (4)

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/s/

SARMISTHA SANYAL
02/28/2023 11:22:05 AM

STANLEY AU
02/28/2023 02:18:10 PM
Team Lead

SEONGEUN CHO
02/28/2023 02:19:36 PM

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)

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

Date of This Review:	November 28, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 216203
Product Name, Dosage Form, and Strength:	(b) (4) ^a (sotagliflozin) tablets, 200 mg and 400 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Lexicon Pharmaceuticals, Inc.
FDA Received Date:	May 27, 2022
TTT ID #:	2022-2261
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

^a Labels and labeling submitted by the Applicant for NDA 216203 includes the previously proposed proprietary name, Inpefa, which was denied on January 28, 2022. Subsequently, the proprietary name, (b) (4) was found conditionally acceptable for NDA 216203 on September 7, 2022. As such, the name (b) (4) is used throughout this review.

1 REASON FOR REVIEW

As part of the approval process for 505(b)(1) NDA 216203 (b) (4) (sotagliflozin) tablets, we reviewed the proposed (b) (4) prescribing information (PI), container labels, and carton labeling and Medication Guide (MG) 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 (b) (4) container labels, professional sample carton labeling, PI, and MG to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We note instances of lack of continuity of product information between the labeling components, ambiguous administration instructions, the use of an error-prone abbreviation, the lack of information for how to manage missed and vomited doses, and missing dose escalation criteria. Thus the labeling components can be revised to support the safe and effective use of the product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed (b) (4) PI, Medication Guide, container label, and carton labeling can be improved to promote the safe and effective use of the product. We provide recommendations for DCN in Section 4.1 and recommendations for Lexicon Pharmaceuticals, Inc. in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. General Recommendations

1. The Latin abbreviation ‘QD’ may be mistaken as Q.I.D and may lead to medication errors. Replace the error-prone abbreviation “QD” where it appears in the PI with the phrase “once daily” to support the safe use of the product.

B. Prescribing Information

1. Dosage and Administration Section

- a. Revise the header “2.2 (b) (4)” to read “*Recommended Dosage*” to use customary terminology.
- b. The statement. “Swallow tablets whole (b) (4)” appears on the container label. We recommend adding this information to Section 2.2 with the following revision to support the safe and effective use of the drug product:

“Swallow tablets whole. Do not cut, crush, or chew tablets.”
- c. Consider adding information informing users of how to manage a missed dose similar to the missed dose information that is provided in the proposed Medication Guide. Include the acceptable interval for taking a missed dose before the next scheduled dose in order to avoid risks associated with taking 2 doses too close together similar to the following:

If a dose of TRADENAME is missed by more than 6 hours, take the next scheduled dose as prescribed the next day. Do not take 2 doses at the same time to make up for the missed dose.
- d. As proposed, there is no information regarding whether or not an additional dose should be taken if vomiting occurs after administration. Consider adding information to inform users on how to proceed if vomiting occurs after administration similar to the following:

If vomiting occurs after taking TRADENAME, do not take an additional dose. Take the next scheduled dose as prescribed the next day.
- e. As proposed, the instruction to administer the daily dose “before the first meal of the day” lacks clarity . Consider adding a specific period within which the daily dose should be taken before the first meal of the day to eliminate ambiguity.

- f. Current instructions state that, (b) (4). However, the duration of treatment and how to determine tolerance at the 200 mg dose level are not provided. Consider providing information on how long a patient should be treated at the 200 mg dose level and what criteria must be met to increase the dose to 400 mg.

2. Dosage Form and Strengths Section

- a. Revise the dosage form and strengths information for improved clarity and brevity as follows:

Tablets:

- 200 mg: blue, film-coated, oval tablets imprinted in black ink with “LX200” on one side.
- 400 mg : yellow, film-coated, oval tablets (b) (4) on one side

3. Medication Guide

- a. In The “How should I take (b) (4)?” section, consider adding additional information informing users of how to manage a missed dose. Provide the acceptable interval between taking a missed dose and the next scheduled dose in order to avoid risks associated with taking 2 doses too close together.
- b. The statement. “Swallow tablets whole (b) (4)” appears on the container label. Add this information to the “How should I take (b) (4)?” section with the following revision to support the safe and effective use of the drug product:

“Swallow tablets whole. Do not cut, crush or chew tablets.”

4.2 RECOMMENDATIONS FOR LEXICON PHARMACEUTICALS, INC.

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

A. Container labels – Bottle

1. Revise the statement “Swallow tablets whole (b) (4)” to read “Swallow tablets whole. Do not cut, crush, or chew tablets.” We recommend this revision to support the safe and effective use of the drug product.
2. In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and

repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.

¹The guidance is available from:

<https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.
4. To ensure consistency with the Prescribing Information, revise the statement, “(b) (4): See prescribing information” to read “Recommended Dosage: See prescribing information.”
5. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.

B. Professional Sample Carton Labeling

1. As proposed, the product strength statement does not clearly communicate the strength is per unit. Revise the strength statement to make it clear that the designated strength is per tablet (i.e. “200 mg per tablet”).
2. Revise the statement “Swallow tablets whole (b) (4)” to read “Swallow tablets whole. Do not cut, crush, or chew tablets.” We recommend this revision to support the safe and effective use of the drug product.
3. To ensure consistency with the Prescribing Information, revise the statement, “(b) (4): See prescribing information” 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 (b) (4) received on May 27, 2022 from Lexicon Pharmaceuticals, Inc..

Table 2. Relevant Product Information for (b) (4)	
Initial Approval Date	N/A
Active Ingredient	sotagliflozin
Indication	To: • Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure. • Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.
Route of Administration	Oral
Dosage Form	tablets
Strength	200 mg and 400 mg
Dose and Frequency	The recommended starting dose of (b) (4) is 200 mg once daily before the first meal of the day. (b) (4) (b) (4)
How Supplied	Bottles of 30 or 90 tablets Professional Sample: 7-count blister pack
Storage	Store at 68°F to 77°F (20°C to 25°C); excursions permitted between 59°F and 86°F (15°C and 30°C) [see USP Controlled Room Temperature]
Container Closure	Commercial: 50 mL, 60 mL, or 100 mL HDPE bottles (b) (4) (b) (4) Professional Sample: (b) (4)-aluminum blister pack

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 (b) (4) labels and labeling submitted by Lexicon Pharmaceuticals, Inc..

- Container label received on May 27, 2022
- Carton labeling received on May 27, 2022
- Professional Sample Blistercards received on May 27, 2022
- Professional Sample Carton Labeling received on May 27, 2022
- Prescribing Information and Medication Guide (Image not shown) received on May 27, 2022, available from <\\CDSESUB1\EVSPROD\nda216203\0021\m1\us\draft-labeling-text.docx>

G.2 Label and Labeling Images



^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/

JANINE A STEWART
11/28/2022 10:55:29 AM

HINA S MEHTA
11/28/2022 11:20:27 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

Date: 11/22/2022 **Date consulted:** 5/27/2022

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

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Cardiology and Nephrology (DCN)

Drug: TRADENAME (sotagliflozin) tablet, for oral use

NDA: 216203

Applicant: Lexicon Pharmaceuticals

Subject: Pregnancy and Lactation Labeling

Proposed

Indication¹: A dual inhibitor of SGLT1 and SGLT 2, indicated to:

- Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure.
- Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.

¹ The Applicant's proposed indication was still being discussed by the DCN Review Team at the time this DPMH review was finalized.

Materials

Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 216203 on December 30, 2021
- Applicant's response on February 21, 2022, to FDA Information Request (IR) on February 18, 2022
- Applicant's submitted background package and proposed labeling for NDA 216203 on May 27, 2022.
- DCN consult form for DPMH, DARRTS Reference ID 5010969

Consult Question:

The review team requests DPMH's input on the labeling to be consistent with the Pregnancy and Lactation Labeling Rule.

INTRODUCTION AND BACKGROUND

- Sotagliflozin is a dual inhibitor of SGLT1 and SGLT 2, which was originally developed by Lexicon Pharmaceuticals and Sanofi (b) (4)
- On March 22, 2018, Sanofi submitted sotagliflozin, under NDA 210934, to the FDA for the proposed indication of treatment of adults with T1DM in combination with insulin. The FDA issued a Complete Response on March 22, 2019, due to increased rate of diabetic ketoacidosis in the treatment population in comparison to the placebo.
- On April 29, 2019, European Medicines Agency (EMA) approved sotagliflozin, under the tradename Zynquista, as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycemic control despite optimal insulin therapy. Zynquista was withdrawn from the European market on March 24, 2022 at the request of the marketing-authorization holder for commercial reasons.
- On January 30, 2020, Sanofi ended its partnership with Lexicon and transferred sponsorship of NDA 210934 to Lexicon.
- On December 30, 2021, Lexicon submitted sotagliflozin under NDA 216203 in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the following proposed indications:
 - Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) worsening heart failure regardless of left ventricular ejection fraction.
 - Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus and chronic kidney disease with other cardiovascular risk factors, including a history of heart failure (b) (4)
- On February 8, 2022, DCN consulted DPMH to assist with development of subsections 8.1 and 8.2 of the product's labeling. An Information Request (IR) was sent on February 16, 2022, to obtain additional information regarding patient (b) (6) in study EFC15194

who had become pregnancy during sotagliflozin treatment exposed in. The applicant replied on February 21, 2022.

- On February 28, 2022, Lexicon voluntarily withdrew the NDA citing (b) (4).
- On May 27, 2022, Lexicon resubmitted NDA 216203 with a revised indication and data analysis included in the SOLOIST and SCORED clinical study report providing direct support of the revised indication. The proposed indications include the following:
 - Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure
 - Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.
- DCN consulted DPMH on July 10, 2022, to assist with the Pregnancy and Lactation subsections of labeling.

Drug Characteristics

Sotagliflozin Characteristics²

Drug Class	Sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2) inhibitor
Mechanism of action	SGLT2 is expressed in the proximal renal tubules and is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. By inhibiting SGLT2, sotagliflozin reduces reabsorption of filtered glucose and thereby promotes urinary glucose excretion. Sotagliflozin is thought to reduce sodium reabsorption and increase the delivery of sodium to the distal tubule. This is thought to influence several physiological functions including, but not restricted to, lowering both pre-load and after-load of the heart, downregulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback. SGLT1 is expressed in the intestine and is the major transporter for glucose absorption. Local intestinal inhibition of SGLT1 delays and reduces glucose absorption in the proximal intestine, resulting in a blunting and delay of postprandial hyperglycemia.
Molecular weight	424.94 Daltons
Half-life	Mean Terminal half-life ranged from 20.9 to 35 hours for sotagliflozin and from 19.2 to 26.0 hours for the metabolite, sotagliflozin-3-O-glucuronide.

² The information in the table is based on the Applicant's proposed labeling, discussion with the DCN Clinical Review Team and personal communications with DCN Pharmacology Toxicology Team on 10/2/22. At the time this DPMH review was completed, there were ongoing discussions by the team regarding the drug's mechanism of action and whether it should be listed as a SGLT1 inhibitor.

Protein Binding	>93% bound in vitro
Bioavailability	25% (90% CI 16% to 29%) for 400mg oral dose

Sotagliflozin is an oral tablet which comes in two dose strengths: 200mg and 400mg. The proposed dose is 200mg once daily before the first meal of the day. It should be increased to 400mg daily in patients tolerating the 200mg dosage.

Serious adverse reactions³

- Ketoacidosis
- Volume depletion
- Urosepsis and pyelonephritis
- Hypoglycemia with concomitant use with insulin and insulin secretagogues
- Necrotizing fasciitis of the perineum (Fourier's Gangrene)
- Genital mycotic infection

PREGNANCY

Heart Failure and Pregnancy⁴

Incidence: About 6.2 million adults in the United States have heart failure (HF).⁵ HF affects both genders equally.⁶

HF is the most common complication of cardiac disease in pregnancy, with a prevalence of 13% reported in a large worldwide registry of women with preexisting cardiac disease to 33% in women with preexisting cardiomyopathy.⁷ In a retrospective community-based cohort study by Ng et al. (2018) between 2003 and 2014, there were 488 cases of heart failure diagnosed in 385,935 pregnancies, which corresponded to 126 cases per 100,000 pregnancies. Peripartum cardiomyopathy was the most common cause accounting for 333 (68.2%) cases.⁸

Cardiomyopathy (11.5%) and other cardiovascular conditions (15.5%) account for 27% of all pregnancy-related deaths in the United States (2014-2017).⁹ In United States, ventricular failure due to peripartum cardiomyopathy occurs in 1/1421 African Americans, 1/2675 Asians, 1/4075

³ Based on applicant proposed labeling and discussion with the Clinical Review Team.

⁴ DeCara JM, et al. Management of heart failure during pregnancy. UpToDate. Accessed 1/26/2022. https://www.uptodate.com/contents/management-of-heart-failure-during-pregnancy?search=pregnancy%20and%20heart%20failure&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

⁵ Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Associationexternal icon. *Circulation*. 2020;141(9):e139-596.

⁶ Bozhkurt B and Khalaf S. Heart Failure in Women. *Methodist Deakey Cardiovasc J*. 2017. 13(4): 216-223.

⁷ Bright R et al. Maternal Heart Failure. *J Am Heart Assoc*. 2021. <https://www.ahajournals.org/doi/epub/10.1161/JAHA.121.021019>

⁸ Ng AT, Duan L, Win T, Spencer HT, Lee MS. Maternal and fetal outcomes in pregnant women with heart failure. *Heart*. 2018 Dec;104(23):1949-1954.

⁹ CDC: Pregnancy Mortality Surveillance System. Accessed 2/7/22. <https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm#causes>

Caucasians, and 1/9861 people of Hispanic origin.¹⁰

Definition: Heart failure, defined as cardiomyopathy with ejection fraction < 30% or New York Heart Association (NYHA) class III or IV heart failure.

Cause: HF is caused by a number of conditions, including left ventricular dysfunction, right ventricular dysfunction, valvular heart disease, pericardial disease, obstructive lesions in the heart or great vessels, or high-output HF.

Pregnancy: HF can occur in pregnancy or peripartum due to exacerbation of existing disease or as new onset disease.

- Pregnancy is associated with substantial hemodynamic changes, including 30 to 50 percent increases in both cardiac output and blood volume. It is often viewed as physiologic stress test. In women with a history of HF or other cardiovascular disorders, these demands can lead to clinical decompensation. Conditions that increase the risk of developing HF during pregnancy include cardiomyopathy (e.g., dilated cardiomyopathy or hypertrophic cardiomyopathy), mitral stenosis, aortic stenosis, and severe mitral or aortic regurgitation
- Women without a history of cardiovascular disease can develop HF due to diseases acquired during pregnancy (e.g., preeclampsia, chronic hypertension, pulmonary hypertension, amniotic fluid embolism), such as peripartum cardiomyopathy.

Pregnancy outcomes: Heart failure is associated with adverse pregnancy outcomes. One international observational registry,¹¹ including 173 HF cases in 1321 pregnant patients with underlying heart disease, reported HF occurred at a median gestational age of 32 weeks with the highest incidence of HF at the end of the second trimester (34%) or peripartum (31%). HF increased maternal mortality from 0.5% to 4.8%. Preeclampsia was strongly related to HF (OR 7.1, 95% CI 3.9 to 13.2, $p<0.001$). Fetal death and the incidence of preterm birth were higher in women with HF compared to those without (4.6% vs 1.2%, $p=0.001$; and 30% vs 13%, $p=0.001$). Birth weight was lower than 2500g in 24% of pregnant patients with HF, and in 13% in patients without HF ($p<0.001$).

Management: Management of women with a history of chronic HF or other cardiovascular disorders focuses on the adjustment of chronic medical therapies and monitoring for decline and clinical decompensation.

Components of therapy of chronic HF include treatment of systemic factors, lifestyle modification, review of drugs, vaccinations (pneumococcal and annual influenza), pharmacologic therapy, and device therapy (including cardiac resynchronization therapy and/or implantable cardioverter-defibrillator therapy). If indicated, implantation procedures for cardiac

¹⁰ Anthony J, et al. Decompensated heart Failure in Pregnancy. Card Fail Rev. 2016 May;2(1):20-26.

¹¹ Ruys TPE, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPACHart 2014;100:231-238.

resynchronization therapy and/or implantable cardioverter-defibrillator therapy are performed prior to or following pregnancy, if possible, to avoid the risk of radiation to the fetus. Drugs used to treat chronic HFrEF during pregnancy include diuretics, beta blockers, hydralazine plus nitrate, and digoxin. Digoxin is an FDA-approved for the treatment of heart failure.

- During pregnancy, clinical HF including pulmonary congestion is treated with a diuretic.
- Beta blockers are generally continued during pregnancy in women with chronic HFrEF who are taking a beta blocker as part of a chronic regimen to improve long-term outcomes.
- For pregnant women with symptoms of HF, vasodilator therapy with hydralazine plus isosorbide dinitrate is added to the medical regimen.
- For pregnant women with symptoms of HF due to systolic dysfunction that persists despite diuresis and vasodilator therapy, digoxin is often added to the medical regimen.

Treatment of HFpEF during pregnancy includes control of systolic and diastolic hypertension, control of pulmonary congestion and peripheral edema with diuretics, and control of heart rate if elevated.

- Antihypertensive agents that may be used to treat HFpEF during pregnancy include beta blockers and heart rate-limiting calcium channel blockers.
- Digoxin is not indicated to treat HFpEF.

REVIEW

Nonclinical Experience

In embryo-fetal development studies in rats and rabbits, sotagliflozin was administered during a time interval that coincided with the first trimester (ie. during the period of organogenesis) in humans.

No developmental toxicities were observed when sotagliflozin was administered at doses up to 100 mg/kg/day in pregnant rats during embryonic organogenesis [40 times the human exposure at the maximum recommended human dose (MRHD)].

In rats, at 350 mg/kg/day, sotagliflozin (161 times the human exposure at the MRHD) caused maternal toxicity (decreased maternal body weight gain; transient decreased food consumption), marked embryo-lethality, effects on fetal growth, and cardiovascular and skeletal fetal abnormalities.

No developmental toxicities were observed in rabbits at doses up to 200 mg/kg/day (9 times the human exposure at the MRHD).

In a prenatal and postnatal development study in pregnant and lactating rats, sotagliflozin was administered at oral doses up to 100 mg/kg/day from gestation Day 6 through to lactation Day 20 (weaning). No sotagliflozin-related adverse effects in pregnant and lactating females and offspring development were observed at exposures that were 40 times the human exposure at the MRHD.

In a juvenile toxicology study in rats, renal changes were observed when sotagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Exposure approximately 5 times (males) and 11 times

(females) the clinical exposure at the maximum recommended human dose (MRHD) of 400 mg QD caused reversible renal tubular dilation. In embryo-fetal development studies, sotagliflozin at 350 mg/kg/day (161 times the human exposure at the MRHD) in rats caused marked embryo-lethality, effects on fetal growth, and cardiovascular and skeletal fetal abnormalities associated with maternal toxicity (decreased maternal body weight gain; transient decreased food consumption); there was no evidence of fetal harm at exposures to sotagliflozin approximately 40 times (rats) and 9 times (rabbits) the human exposure at the MRHD.

The reader is referred to full Pharmacology/Toxicology report by Baichun Yang, Ph.D. and Xuan Chi, Ph.D.

Reviewer comment:

The finding of reversible dose-related increase in renal tubular dilations has been confirmed in discussion with the Pharmacology Toxicology Team. This finding is consistent with animal findings observed in juvenile animal studies conducted with other SGLT-2 inhibitors. The following has been observed with other SGLT-2 inhibitors:

- *Dapagliflozin¹²: Direct administration of dapagliflozin to juvenile rats at a dose that is 15 times the clinical dose, during a period of development corresponding to late second and third trimester of human pregnancy, resulted in adverse renal pelvic and tubule dilation. These renal findings were not fully reversible within a 1-month recovery period.*
- *Canagliflozin¹³: Direct administration of canagliflozin to juvenile rats at a dose that is 0.5 times the clinical dose, during a period of development corresponding to late second and third trimester of human pregnancy, resulted in increased kidney weights and a dose dependent increase in the incidence and severity of renal pelvic and tubular dilation. These renal findings were not fully reversible within a 1-month recovery period.*
- *Empagliflozin¹⁴: Direct administration of empagliflozin to juvenile rats at a dose that is approximately 13 times the maximum clinical dose, during a period of development corresponding to late second and third trimester of human pregnancy, resulted in an increase in kidney weights and renal pelvic and tubular dilation. These renal findings were reversible within a 13-month recovery period.*
- *Ertugliflozin¹⁵: Direct administration of ertugliflozin to the juvenile rats at a dose that was approximately 13 times the maximum clinical dose during a period of development corresponding to late second and third trimester of human pregnancy, resulted in renal tubule and renal pelvis dilation and renal mineralization. These findings were partially reversible within a 1-month recovery period.*

¹² Approved labeling for dapagliflozin, NDA 202293. Drugs@FDA accessed 11/18/2022

¹³ Approved labeling for canagliflozin, NDA 204042. Drugs@FDA accessed 11/18/2022

¹⁴ Approved labeling for empagliflozin, NDA 204629. Drugs@FDA accessed 11/18/2022

¹⁵ Approved labeling for ertugliflozin, NDA 209803. Drugs@FDA accessed 11/18/2022

Review of Clinical Trials

Pregnant women were excluded from the clinical trials with sotagliflozin. There were no pregnancies that occurred during the SOLOIST¹⁶ or SCORED¹⁷ trials. The mean age of the participants for the SOLOIST and SCORED trials was ≥ 63 years.

Thirty pregnancies were reported in the clinical trials according to Sponsor's Table 14 in the submission titled "Summary of Clinical Safety." The reader is referred to Appendix A of this review. Five duplicated cases were present.

- 15 were unexposed (included maternal or paternal exposures) to sotagliflozin and exposed to placebo. Four duplicate cases were present ((b) (6) in LX4211.312, (b) (6) in LX4211.312, (b) (6) in LX4211.310, (b) (6) in LX4211.310)
 - 7 live births (1 birth with congenital malformations: atrial septal defect)
 - 2 terminations
 - 1 spontaneous abortion
 - 1 stillbirth
- 1 was a paternal exposure to an active comparator. This resulted in a live birth.
- 14 were exposed to sotagliflozin.
 - 4 were paternal exposures.
 - 3 live births
 - 1 unknown outcome
 - 10 were maternal exposures. All exposures occurred during the first trimester of pregnancy. One was a duplicated case (patient (b) (6)). See Table 1 below.
 - 2 terminations¹⁸
 - 1 spontaneous abortion
 - 1 ongoing pregnancy
 - 5 livebirths

Table 1. Reviewer's Table of Pregnancy Outcomes of Maternally Exposed Sotagliflozin Pregnancies in the Clinical Trials¹⁹

Trial	Patient #	Sotagliflozin ²⁰	PT terms	Exposure	Outcome
T1DM					
LX4211.206	(b) (6)	200 mg	Pregnancy	1 st trimester	Term Live birth/No major congenital malformation (MCM)
LX4211.309		400mg	Exposure during pregnancy	1 st trimester	Term Live birth/No MCM
LX4211.310		200mg	Exposure during pregnancy	1 st trimester	Birth outcome not described in the narrative, but listed as live birth

¹⁶ SOLOIST Trial: Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure trial

¹⁷ SCORED Trial: Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk trial

¹⁸ One of the terminations should be categorized as a spontaneous abortion, see Table 1, patient # (b) (6)

¹⁹ Based on Applicant's Submission Table 4 of the Summary of Clinical Safety (Appendix A)

²⁰ Based various safety reports under NDA 210934 and NDA 216203

LX4211.312	(b) (6)	400mg	Exposure during Pregnancy Abortion Inducted	1 st trimester	Pregnancy Termination
LX4211.312	(b) (6)	400mg	Exposure during pregnancy	1 st trimester	On going
T2DM					
BEQ14993	(b) (6)	400mg	Pregnancy	1 st trimester	Pregnancy Termination*
EFC14868	(b) (6)	400mg	Pregnancy	1 st trimester	Live birth, ²¹ no MCM
EFC14833	(b) (6)	400mg	Pregnancy, Abortion Spontaneous	1 st trimester	SAB
EFC15194	(b) (6)	400mg	Pregnancy	1 st trimester and slightly into second trimester (6 ⁺² to 14 ⁺⁴ weeks)	Live birth term/NICU admission for low blood sugar in baby.

* Although this case was listed as a termination because the patient took misoprostol 800mg every 4 hours, the patient was previously diagnosed with threatened abortion with human chorionic gonadotropin trending downward and confined placental mosaicism.

† This case was reported twice.

The applicant concludes that in the limited number of reports received involving pregnancy, there were no safety issues identified with sotagliflozin.

Review of Literature

Applicant Review of Literature

The applicant conducted a review of published literature regarding SGLT use in pregnancy and was unable to locate any information on pregnancy outcomes following SGLT inhibitor use.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,²² ReproTox,²³ Shepard's)²⁴ regarding sotagliflozin use in pregnancy.

- There are no published data on the use of sotagliflozin in pregnancy.

Reviewer comment:

The available human data regarding the use of sotagliflozin in pregnancy are insufficient to assess for a drug-related risk of congenital malformations, miscarriage, or adverse maternal or fetal outcomes. Based on embryofetal developmental study, developmental toxicities were not

²¹ It is unclear if this is a preterm birth since the reported LMP does not match the EDC and the reported EDC could on result in a positive pregnancy test by the report date of pregnancy. See page 501 of the EFC 14868 Medwatch forms.

²² Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 8/30/2021.

²³ ReproTox Website: www.Reprottox.org. REPROTOX was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/30/21.

²⁴ 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 8/30/2021.

observed when sotagliflozin was administered a dose of 40x the MRHD and 9X the MRHD in rats and rabbits, respectively. Developmental toxicities were not observed in rats in pre- and postnatal development study at a dose of 40X the MRHD.

However, direct administration of sotagliflozin to juvenile rats from postnatal day (PND) 21 until PND 90 resulted in reversible dose-related increases in kidney weights for males given ≥ 10 mg/kg/day and females given ≥ 30 mg/kg/day and was correlated with renal tubular dilation for animals given ≥ 30 mg/kg/day. This information was confirmed in discussion with the Pharmacology Toxicology Review Team.

In general, there are concerns regarding the use of SGLT2 inhibitors during the second and third trimesters of pregnancy secondary due to animal findings. Increased incidence and severity of renal pelvic dilation was found in juvenile animal studies in dapagliflozin, canagliflozin, ertugliflozin, and empagliflozin during a time period that corresponds to second and third trimester of human pregnancy. This change is reversible in empagliflozin after observation for 13 weeks, but only partially reversible in ertugliflozin, canagliflozin, and dapagliflozin after observation for one month. Similar to other SGLT2 inhibitors, direct administration of sotagliflozin to juvenile rats also resulted in a finding of renal tubular dilation. Therefore, similar to other SGLT2 inhibitors, sotagliflozin should not be used during second and third trimesters of 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

In rats, after a single oral dose of radiolabeled sotagliflozin to dams on gestation Day 13 or 18, low to moderate levels of radioactivity were present in fetal tissues. In rat milk, the mean milk/plasma concentration ratios ranged from 0.458 to 2.04. Exposure to radioactivity was approximately 1.3-fold greater in milk than in plasma based on AUC_{0-inf} values.

The reader is referred to full Pharmacology/Toxicology report by Baichun Yang, Ph.D. and Xuan Chi, Ph.D.

Review of Literature

Applicant Review of Literature

The applicant did not find any relevant literature on the use of sotagliflozin during lactation in humans.

Since sotagliflozin is present in animal milk and based on the findings of the juvenile rat studies that demonstrate reversible renal tubular dilation, the applicant concludes that women should be advised against breastfeeding during sotagliflozin therapy.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and reference sites

(Micromedex,²⁵ LactMed,²⁶ Brigg's,²⁷ and Hales²⁸) regarding sotagliflozin use in lactation, and no information was found.

Reviewer comment:

Sotagliflozin is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. There are no data on the effect of the sotagliflozin on the breastfed infant or milk production.

There is a class-related concern regarding SGLT2 inhibitors and adverse effects on renal development related to pre- and postnatal development studies and juvenile toxicology studies in rats. Because human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, and, since lactation is not recommended for this class of drugs,^{29,30,31} use of sotagliflozin during breastfeeding is not recommended.

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

Carcinogenesis

In the 6-month transgenic RasH2 mouse carcinogenicity study, no sotagliflozin-related proliferative changes (neoplasia and hyperplasia) were observed at doses up to 100 mg/kg/day. In the rat carcinogenicity study with sotagliflozin up to 350 mg/kg/day, there were no treatment-related neoplasms in male (up to 15X MHRD) and female (up to 45X MHRD) animals.

Mutagenesis

Sotagliflozin was not mutagenic or clastogenic, with or without metabolic activation, in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* Chinese hamster ovary cell chromosomal aberration study, and an *in vivo* micronucleus assay in rats.

Impairment of Fertility

Sotagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at doses up to 300 mg/kg/day, which represents an exposure multiple of 55 times the human exposure at the MRHD in both males and females.

²⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 2/15/2022.

²⁶ <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 2/15/22.

²⁷ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015.

²⁸ Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

²⁹ Approved labeling for Farxiga (dapagliflozin), NDA 202293, at Drugs@FDA. Last updated 4/30/21

³⁰ Approved labeling for Invokana (canagliflozin), NDA 204042, at Drugs@FDA. Last updated 8/18/20

³¹ Approved labeling for Glyxambi (empagliflozin and linagliptin), NDA 206073, at Drugs@FDA. Last updated 3/21/22.

The reader is referred to full Pharmacology/Toxicology report by Baichun Yang, Ph.D. and Xuan Chi, Ph.D.

Review of Literature

Applicant Review of Literature

The applicant did not find any relevant literature on adverse effects of sotagliflozin on fertility.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and the reference sites regarding adverse effects of sotagliflozin on fertility. No information was found.

Reviewer comment:

There are no data regarding the effect of sotagliflozin on human fertility. Animal reproductive studies did not show sotagliflozin adversely affecting fertility in rats. Sotagliflozin is not mutagenic or clastogenic. Sotagliflozin was not considered to be carcinogenic in rats at ≤ 30 mg/kg/day. The exposure multiples at 30 mg/kg/day were approximately 8-fold and 21-fold that of the MRHD for males and females, respectively. This was confirmed in discussion with the DCN Pharmacology Toxicology Team. 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

The available human data regarding the use of sotagliflozin in pregnancy are insufficient to assess a drug-related risk of congenital malformations, miscarriage, or adverse maternal or fetal outcomes. Based on animal reproduction studies, sotagliflozin was not associated embryofetal toxicity in rabbits at 9 times the MRHD when administered in embryofetal development study. In rats, sotagliflozin was not associated embryofetal toxicity at 40 times the human exposure at the MRHD in rats in embryofetal developmental study and pre- and postnatal development study.

In general, there are concerns regarding the use of SGLT2 inhibitors during the second and third trimesters of pregnancy due to an increased incidence and severity of renal pelvic dilation in F1 rats in pre and postnatal developmental studies and juvenile toxicology studies. Although renal tubular dilation was not found in the pre- and post-developmental study for sotagliflozin, like other SGLT 2 inhibitors, renal tubular dilation was found in juvenile rats when sotagliflozin was directly administered to juvenile rats (≥ 30 mg/kg/day from PND 21 to PND 90). Because of the concern for this class of drugs, DPMH recommends that sotagliflozin not be used during the second and third trimesters of pregnancy.

Sotagliflozin is unlikely to be used commonly in pregnancy because there are safety concerns regarding the use of SGLT2 inhibitors during the second and third trimesters of pregnancy based on animal studies. Additionally, the proposed indicated population include patients with heart failure, which is not common during pregnancy. The average age of clinical trial participants in SOLOIST and SCORED trials were 69 years old in the sotagliflozin arm. The incidence of HF in pregnancy is approximately 126 cases per 100, 000 pregnancies according to a 2018 study.⁷

Based on the number pregnancies that occur per year (6.3 million pregnancies³² and 3.6 million birth per the Centers for Disease Control and Prevention³³) in the US, this results in approximately 4500 to 8000 pregnancies per year. However, 68.1% of all cases of heart failure were peripartum cardiomyopathy, which are mostly diagnosed during the postpartum period. Because there are insufficient data regarding sotagliflozin use in pregnancy and sotagliflozin is not likely to be used commonly during pregnancy, DPMH recommends a postmarketing descriptive pregnancy safety study to collect this information. Additionally, DPMH recommends that the applicant submit a summary of sotagliflozin utilization rates amongst females of reproductive potential (females aged 15 to 50 years) calculated cumulatively from the time of initial approval, two to three years postmarketing. If it appears that use of sotagliflozin is high in females of reproductive potential, then the Agency will consider if it is appropriate to issue a PMR for a pregnancy registry study at that time.

Lactation

Sotagliflozin is present in animal milk. When a drug is present in animal milk, it is likely to be present in human milk. There are no data on the effect of the sotagliflozin on the breastfed infant or milk production.

There is a class-related concern regarding SGLT2 inhibitors and adverse effects on renal development related to pre- and postnatal development studies and juvenile toxicology studies in rats. Because human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, and, since lactation is not recommended for this class of drugs, use of sotagliflozin during breastfeeding is not recommended. Because we do not have information on whether this drug is transferred into human milk, it would be informative to conduct a milk-only study in lactating volunteer to determine the concentration of sotagliflozin in milk. DPMH recommends a postmarketing clinical lactation study (milk-only) to inform the lactation labeling.

Females and Males of Reproductive Potential

There are no data regarding the effects of sotagliflozin on human fertility. Animal reproductive studies did not show sotagliflozin adversely effecting fertility in rats. Sotagliflozin is not mutagenic or clastogenic. Sotagliflozin did not cause carcinogenicity in rats at ≤ 30 mg/kg/day. There is no anticipated drug-to-drug interaction between sotagliflozin and hormonal contraceptives. DPMH recommends omitting subsection 8.3 from the labeling.

POSTMARKETING REQUIREMENT (PMR) RECOMMENDATIONS

- Conduct prospective pregnancy safety study to obtain pregnancy safety data in individuals exposed to sotagliflozin during pregnancy. The primary outcome of the study will be major congenital malformations (MCMs). Additional outcomes include spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational age infants, and other adverse maternal or fetal outcomes, including infant postnatal growth and development through the first year of life.

³² NCHS data Brief No. 136 December 2013. [Products - Data Briefs - Number 136 - December 2013 \(cdc.gov\)](https://www.cdc.gov/products-data/briefs/136) Accessed 9/19/22.

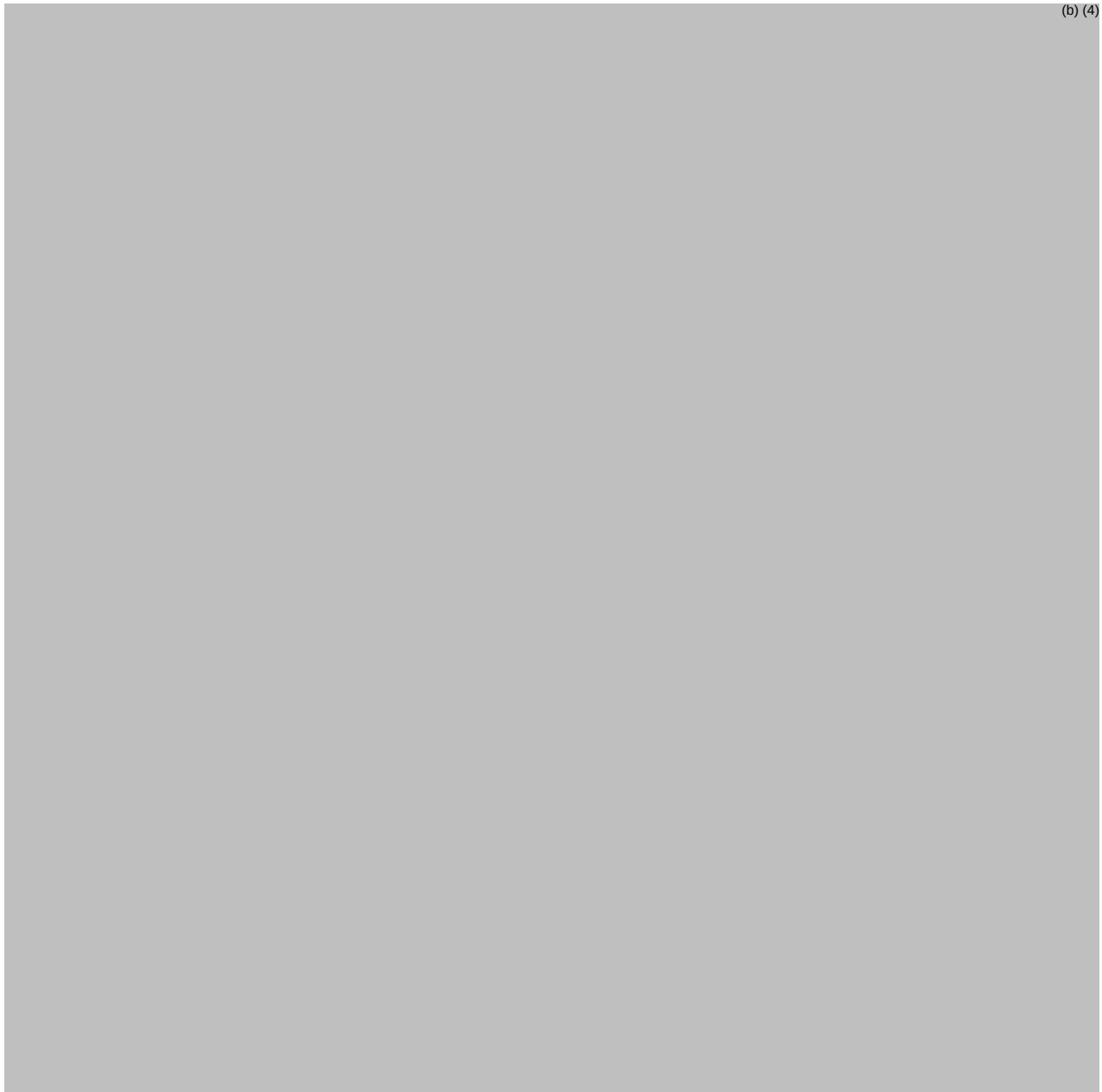
³³ [National Vital Statistics System - Birth Data. www.cdc.gov/nchs/nvss/births.htm](https://www.cdc.gov/nchs/nvss/births.htm). Accessed 9/19/2022.

- Perform a lactation study (milk only) in lactating volunteers to assess concentrations of sotagliflozin in breast milk using a validated assay and to assess the effects on the breastfed infants.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling



(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

APPENDIX A. Pregnancy Outcomes from the Clinical Trials³⁴

Table 14: Pregnancy Events in Patients who were Treated with Sotagliflozin and Their Partners

Indication Study	Patient #	Randomization	SOC (System Organ Class)	PT (Preferred Term)	Outcome
T1DM					
LX4211.206	(b) (6)	Sotagliflozin	Pregnancy, puerperium and perinatal conditions	Pregnancy	Live birth
LX4211.309		Sotagliflozin	Injury, poisoning and procedural complications	Exposure during pregnancy	Live birth
LX4211.310		Sotagliflozin	Injury, poisoning and procedural complications	Exposure during pregnancy	Live birth
LX4211.312		Sotagliflozin	Injury, poisoning and procedural complications	Exposure during pregnancy	Live birth
LX4211.310		Sotagliflozin	Social circumstances	Pregnancy of partner	Live birth
LX4211.310		Sotagliflozin	Social circumstances	Pregnancy of partner	Outcome of pregnancy unknown
LX4211.312		Sotagliflozin	Injury, poisoning and procedural complications	Exposure during pregnancy	Induced abortion
LX4211.312		Sotagliflozin	Surgical and medical procedures	Abortion induced	Recovered
LX4211.312		Placebo	Injury, poisoning and procedural complications	Exposure during pregnancy	Live birth
LX4211.312		Placebo	Injury, poisoning and procedural complications	Exposure during pregnancy	Live birth; Baby born with Atrial Septal Defect
LX4211.312		Placebo	Injury, poisoning and procedural complications	Exposure during pregnancy	Baby case: Atrial Septal Defect; Congenital Pneumonia; Left ventricular hypertrophy
LX4211.312		Placebo	Social circumstances	Pregnancy of partner	Live birth
LX4211.312		Placebo	Social circumstances	Pregnancy of partner	Live birth
LX4211.312		Placebo	Social circumstances	Pregnancy of partner	Live birth
LX4211.310		Placebo	Injury, poisoning and procedural complications	Exposure during pregnancy	Abortion induced
LX4211.310		Placebo	Pregnancy, puerperium and perinatal conditions	Abortion	Recovered
LX4211.312		Placebo	Social circumstances	Pregnancy of partner	Abortion spontaneous
LX4211.312		Placebo	Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	Not Applicable

³⁴ Applicant's Table 14 under Summary of Clinical Safety.

Indication Study	Patient #	Randomization	SOC (System Organ Class)	PT (Preferred Term)	Outcome
LX4211.310	(b) (6)	Placebo	Social circumstances	Pregnancy of partner	Stillbirth
LX4211.310		Placebo	Pregnancy, puerperium and perinatal conditions	Stillbirth	Baby deceased in utero at 36 weeks and 4 days gestation.
T2DM					
EFC14868		Sotagliflozin	Pregnancy, puerperium and perinatal conditions	Pregnancy	Live birth
BEQ14993		Sotagliflozin	Pregnancy, puerperium and perinatal conditions	Pregnancy	Induced abortion
EFC14833		Sotagliflozin	Pregnancy, puerperium and perinatal conditions	Pregnancy	Abortion spontaneous
EFC14833		Sotagliflozin	Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	Recovered
EFC14838		Active comparator	Social Circumstances	Pregnancy of partner	Live birth
EFC14833		Placebo	Pregnancy, puerperium and perinatal conditions	Pregnancy	Live birth
EFC14834		Placebo	Pregnancy, puerperium and perinatal conditions	Pregnancy	Live birth
T2DM China					
EFC15194		Sotagliflozin	Social Circumstances	Pregnancy of partner	Live birth
EFC15194		Sotagliflozin	Pregnancy, puerperium and perinatal conditions	Pregnancy	Live birth
EFC15194		Study drug not given	Pregnancy, puerperium and perinatal conditions	Pregnancy	Elective Abortion

Source: individual clinical study reports

PT = preferred Term, SOC = system organ class; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

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/s/

WENJIE SUN
11/22/2022 09:55:57 AM

MIRIAM C DINATALE
11/22/2022 11:50:55 AM

LYNNE P YAO
11/22/2022 12:57:07 PM

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

DATE: 10/5/2022

TO: Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216203

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in November 2021, which falls within the surveillance interval. The inspection was conducted under the following submission:

(b) (4).

The final classification for the inspection was No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	(b) (4)	

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/s/

JAMES J LUMALCURI
10/05/2022 02:39:27 PM