CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216203Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	216203
PDUFA Goal Date	May 27, 2023
Nexus TTT #	2022-2262, 2022-2260
Reviewer Name(s)	Courtney Cunningham, PharmD
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Review Completion Date	May 25, 2023
Subject	Evaluation of Need for a REMS
Established Name	Sotagliflozin
Trade Name	Inpefa
Name of Applicant	Lexicon Pharmaceuticals, Inc.
Therapeutic Class	Sodium-glucose cotransport inhibitor
Formulation(s)	200 mg and 400 mg film-coated oral tablets
Dosing Regimen	200 mg by mouth once daily increased to 400 mg once daily as tolerated

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Inpefa (sotagliflozin) is necessary to ensure the benefits outweigh its risks. Lexicon Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 216203 for sotagliflozin. The approved indication for sotagliflozin will be 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. The serious risks associated with sotagliflozin include the following: ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum, and genital mycotic infections.[1] The applicant did not submit a REMS with this application but provided a rationale as to why the proposed labeling serves as appropriate risk mitigation.

DRM and the Division of Cardiology and Nephrology (DCN) have determined that a REMS is not needed to ensure the benefits of sotagliflozin outweigh its risks. As with other sodium-glucose cotransporter (SGLT) 2 inhibitors, the risks of ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum, and genital mycotic infections will be mitigated through labeling. Given the similarity of the risks associated with sotagliflozin and other SGLT2 inhibitors, additional risk mitigation measures beyond labeling are not necessary to ensure the benefits outweigh the risks of sotagliflozin.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] sotagliflozin is necessary to ensure the benefits outweigh its risks. Lexicon Pharmaceuticals, Inc. (Lexicon) submitted a New Drug Application (NDA) 216203 for sotagliflozin with the proposed indication to 1) reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) worsening heart failure regardless of left ventricular ejection fraction, and 2) 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) This application is under review in the Division of Cardiology and Nephrology (DCN). The applicant did not submit a REMS with this application but provided a rationale as to why the proposed labeling serves appropriate risk mitigation.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2. Background

2.1. Product Information

Sotagliflozin, a new molecular entity, is proposed as a dual sodium-glucose cotransporter (SGLT) 1 and 2 inhibitor to reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) worsening heart failure regardless of left ventricular ejection fraction, and to 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). Inhibiting intestinal SGLT1 stimulates peptides and delays glucose absorption from the intestines, and inhibition of SGLT2 causes a decrease in glucose reabsorption in the proximal renal tubules, leading to urinary glucose excretion and osmotic diuresis. Sotagliflozin is proposed as 200 mg and 400 mg film-coated tablets, dosed initially as 200 mg orally daily which may be increased to 400 mg daily as tolerated.[b]

Sotagliflozin received EMA market approval on April 26, 2019, for an indication for patients with type 1 diabetes, body mass index (BMI) $\geq$ 27 kg/m2, and inadequate glucose control with optimal insulin therapy. However, on March 22, 2022, marketing authorization was withdrawn by the European Commission (EU) at the request of the marketing authorization holder as they were not going to market in the EU due to commercial reasons. Sotagliflozin also received marketing approval for the same indication from Great Britain Medicines and Healthcare Products Regulatory Agency on January 25, 2022, but the product is not currently marketed in Great Britain.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216203 relevant to this review:

- 03/22/2019: Sotagliflozin (NDA 210934) received a Complete Response to treat type 1 diabetes mellitus due to an unfavorable benefit-risk profile; while it modestly decreased hemoglobin A1c, it had a significant, dose-responsive increase of risk of diabetic ketoacidosis[2]
- 07/14/2021: Applicant informed in pre-NDA (IND 135095) meeting background document that "at this time and based on the information currently available, we do not believe a REMS will be necessary"[3] for sotagliflozin if submitted for a proposed indication to 1) reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) worsening heart failure regardless of left ventricular ejection fraction, and 2) 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

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

disease with other cardiovascular risk factors, including a history of heart failure (b) (4)

- 12/30/2022: NDA 216203 submission with the proposed indication to reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) worsening heart failure regardless of left ventricular ejection fraction, and 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) received
- 02/2022: On February 1 and 22, 2022, the applicant notified the Agency that (b) (4) The applicant sent a request to the Agency to withdraw the application on February 27, 2022. The Agency responded that the application was withdrawn on February 28, 2022, (b) (4) prior to resubmission[4]
- 05/27/2022: NDA 216203 submission to: reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) (b) (4) worsening heart failure regardless of left ventricular ejection fraction, and 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) received
- 03/16/2023: Applicant was notified by the Agency in Late Cycle Meeting Minutes that "no issues related to risk management had been identified to date"[5]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Heart failure is a "complex clinical syndrome composed of signs and symptoms that result from any structural or functional impairment of ventricular filing or ejection of blood" in the American Heart Association (AHA)/ American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) 2022 Guideline for Management of Heart Failure.[6] Heart failure is a significant cause of morbidity in the

United States, affecting an estimated 6 million adults. [c,7] Men with diabetes have a greater than two-fold increased risk of developing heart failure and women with diabetes are at greater than a five-fold increase risk of developing heart failure, due to the effects of abnormal cardiac management of glucose and free fatty acids and the metabolic abnormalities of diabetes.[d] Some medications used to treat diabetes also include the risk of mortality and hospitalization for heart failure in diabetic patients, regardless of previous heart failure diagnosis.[8]

3.2. Description of Current Treatment Options

Per the 2022 AHA/ACC/HFSA Guideline for Management of Heart Failure, patients with type 2 diabetes and cardiovascular disease or at high cardiovascular risk are recommended to start SGLT2 inhibitors to prevent hospitalization from heart failure. Clinical management of heart failure is determined by degree of functional impairment, as evidenced by left ventricular ejection fraction (LVEF), and symptoms. The following drugs and/or drug classes are currently approved to treat heart failure with reduced LVEF and shown to decrease hospitalization/prolong survival include the following: hydralazine/isosorbide dinitrate, ivabradine, digoxin, vericiguat, beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, angiotensin receptor and neprilysin inhibitors, and the SGLT2 inhibitors dapagliflozin and empagliflozin. If patients have LVEF reduction, therapy consists of both pharmaceutical options and cardiac devices including ICDs (implantable cardioverter-defibrillator), a cardiac resynchronization (CRT) device with a biventricular pacing, or CRT with defibrillation. No devices are currently approved for patients with normal LVEF.[6]

Empagliflozin is indicated to reduce hospitalization and cardiovascular death in adults with heart failure and reducing the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease. Empagliflozin carries warnings and precautions for ketoacidosis, volume depletion, urosepsis and pyelonephritis, necrotizing fasciitis of the perineum, genital mycotic infections, and hypersensitivity reactions.[9] Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes, and either established cardiovascular disease or multiple cardiovascular risk factors and to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). The warnings and precautions listed in dapagliflozin include ketoacidosis in patients with diabetes mellitus, volume depletion, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum, and genital mycotic infections.[10]

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

4. Benefit Assessment

The clinical reviewer states in the Joint Clinical and Statistical Review of Sotagliflozin on March 23, 2023, that the data submitted in support of NDA 216203 "meets the statutory requirement for substantial evidence of effectiveness…".[11]

To support the proposed indication, the applicant submitted two pivotal, Phase 3 trials, SOLOIST (EFC15156, NCT03521934) and SCORED (EFC14875, NCT03315143). Both trials used the same primary composite endpoint of cardiovascular (CV) death, hospitalization (both first and subsequent) for heart failure (HHF), and urgent heart failure visit (UHFV) in patients with type 2 diabetes mellitus. SOLOIST was a randomized, placebo-controlled, double-blind trial evaluating the safety and efficacy of sotagliflozin in subjects who had been admitted to the hospital, a heart failure unit, infusion center, or emergency room for worsening heart failure with intravascular volume overload. SOLOIST randomized 1,222 subjects in a 1:1 ratio to receive placebo or 200 mg sotagliflozin daily. Sotagliflozin was to be up titrated to 400 mg daily by month 8. SCORED was a randomized, double-blind, placebo-controlled trial that randomized 10,584 subjects who had type 2 diabetes mellitus, chronic kidney disease with estimated glomerular filtration rate (eGFR) $\geq$25 to $\leq$60 mL/min/1.73 m^2, and either a major CV risk factor or were age >55 years with 2 minor CV risk factors. Study treatment in SOLOIST was planned to continue until 1341 positively adjudicated composite events in the total study population and 947 positively adjudicated events in subjects with LVEF <50%. Study treatment in SCORED was planned to continue until 844 positively adjudicated CV death or HHF events and 1189 positively adjudicated 3-point MACE events. Both studies were terminated early due to financial reasons and the applicant's inability to capture the planned quantity of adjudicated events.[11,12]

Subjects taking sotagliflozin in the SOLOIST trial had a decrease in incidence of the composite endpoint with a hazard ratio (HR) of 0.67 (p <0.001, 95% confidence interval (CI) 0.53, 0.85). Subjects in SCORED had decreased incidence of the primary composite endpoint with a HR of 0.75 (p < 0.0004, 95% CI 0.63, 0.88). In both trials, the component with the largest treatment effect was HHF (HR 0.65 (95% CI 0.49, 0.97).[e]

In the November 17, 2022, midcycle communication, the Agency requested the applicant provide justification for the proposed indication for adults with heart failure but were not diabetic. In the December 15, 2022, response from the applicant, the HR of subjects with hemoglobin A1c (HbA1C) $\leq$ 7.1% using sotagliflozin versus placebo in SOLOIST was 0.73 (95% CI 0.51, 1.04) and in subjects with HbA1C >7.1, the HR was 0.65 (95% CI 0.47, 0.92). In the clinical review, the clinical reviewer noted that it is reasonable to extrapolate the presence of a treatment effect on subjects with HbA1C <7.1%.[11,13]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5. Risk Assessment & Safe-Use Conditions

Safety concerns for sotagliflozin are similar to those seen with other SGLT2 inhibitors, and appear to be a class-effect, as opposed to specific to sotagliflozin. Products that are SGLT1 inhibitors typically demonstrate calcium overload due to glucose malabsorption, and sotagliflozin demonstrated a lower state of glucose malabsorption, similar to SGLT2 inhibitors, as opposed to a mixed SGLT1/2 inhibitor.

The serious adverse events (SAEs) in SOLOIST with a risk difference >0.5% were hypotension and hypoglycemia, which is not unexpected with the use of SGLT2 inhibitors, and in SCORED, no SAEs were reported to have a greater than 0.5% risk difference. The treatment-emergent adverse events (TEAEs) with >1% risk difference in SOLOIST were diarrhea, hypotension, fatigue, hypoglycemia, and dysuria. No TEAEs were found to have >1% risk difference in SCORED. [f]

In the March 23, 2023 Joint Clinical and Statistical Review, the clinical reviewer noted that "the safety evaluation of sotagliflozin in SOLOIST and SCORED was adequate and acceptable" for the indication.[11] As with other SGLT2 inhibitors, the serious adverse reactions of ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum, and genital mycotic infections will be mitigated through warnings and precautions in labeling.

5.1. Deaths

In SOLOIST, there was a 7% overall death rate in the study, with the placebo arm having a 7.3% death rate and the sotagliflozin arm having a 6.7% death rate. In SCORED, the 2.6% death rate in the placebo arm and 2.2% in the sotagliflozin arm comprised the 2.4% overall death rate. [g]

5.2. Ketoacidosis

Events of diabetic ketoacidosis were increased in both SOLOIST and SCORED. In SOLOIST, the incidence rate of events was 1.0 per 100 patient-years in the sotagliflozin arm and 1.7 per 100 patient-years in the placebo arm. In SCORED, the incidence rate of events was 0.7 per 100 patient-years in the sotagliflozin arm and 0.5 per 100 patient-years in the placebo arm. In SCORED, the relative risk of DKA was 1.6 (95% CI 1.0, 2.5). There was also a fatal case of DKA in a 70-year-old male in the sotagliflozin arm of SCORED. This patient's primary cause of death was adjudicated as a myocardial infarction. The risk of DKA will be listed in the warnings and precautions of the prescribing information.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.3. Volume Depletion

Subjects taking sotagliflozin reported volume depletion in both trials. In SOLOIST, volume depletion events occurred in 9.3% of the sotagliflozin group and 8.8% of the placebo group. One 66-year-old male treated with sotagliflozin in SOLOIST died from circulatory collapse, and while circulatory collapse was an adverse event of special interest under volume depletion, the death was not due to volume depletion. In SCORED, volume depletion was reported in 5.2% of the subjects using sotagliflozin and 4.0% of subjects taking placebo. In both trials, these events of volume depletion occurred more often in elderly subjects and subjects with lower eGFR at baseline. This will be included in warnings and precautions in the prescribing information.

5.4. Urosepsis and Pyelonephritis

The risk of urosepsis and pyelonephritis that required hospitalization has been reported in SGLT2 inhibitors. Patients who report urinary tract infection symptoms should be evaluated and treated promptly. This information will be included in the warnings and precautions of sotagliflozin's labeling, as it is with other SGLT2 inhibitors.

5.5. Hypoglycemia with Concomitant Use of Insulin and Insulin Secretagogues

Severe hypoglycemia occurred during SOLOIST at rates of 1.7% in sotagliflozin treated subjects and 1.0% in subjects using placebo. In SCORED, severe hypoglycemia occurred at rates of 1.2% in sotagliflozin treated subjects and 1.3% in subjects using placebo. SGLT2 inhibitors carry a risk of hypoglycemia, particularly in combination with insulin or insulin secretagogues. This risk, as with other SGLT2 inhibitors, will be managed in warnings and precautions in the prescribing information.

5.6. Necrotizing Fasciitis of the Perineum

Necrotizing fasciitis of the perineum, or Fournier's gangrene, was originally identified by the FDA as a potential serious adverse event associated with the use of SGLT2 inhibitors in 2018.[11] Three events of Fournier's gangrene in 3 patients occurred in subjects using sotagliflozin in SOLOIST. Two of the three events were categorized as severe. While there was not a significant difference in SCORED between rates of Fournier's gangrene in subjects taking sotagliflozin or placebo, the risk will be included in the warnings and precautions in sotagliflozin prescribing information.

5.7. Genital Mycotic Infection

Genital mycotic infections occurred more commonly in women in both SCORED and SOLOIST, with a greater occurrence in sotagliflozin subjects. In SOLOIST, 0.8% of subjects using sotagliflozin experienced an infection, while 0.2% of subjects taking placebo had a genital mycotic infection. In SCORED, 2.4% of subjects using sotagliflozin experienced an infection, while 0.9% of subjects taking placebo had a genital

mycotic infection. This is a known adverse event with SGLT2 inhibitor use and will be managed in warnings and precautions in the prescribing information as in other SGLT2 inhibitors.[11,14]

6. Expected Postmarket Use

Sotagliflozin is expected to be prescribed primarily by endocrinologists or cardiologists, who are expected to be familiar with the risks of SGLT2 inhibitors. These practitioners are expected to be familiar with appropriate management of adverse events and meet on a regular basis with patients with type 2 diabetes and/or heart failure. Sotagliflozin will be used primarily as an outpatient oral product.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sotagliflozin beyond routine pharmacovigilance and labeling.

7.1. Other Proposed Risk Management Activities

As of the time of this review, no further postmarketing requirements or commitments were planned.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of sotagliflozin on the basis of the efficacy and safety information currently available.

Heart failure is a chronic condition that decreases patients' quality of life and can cause increased pill burden, hospitalizations, and death. Patients with type 2 diabetes are at an increased risk of heart failure, especially females. Like other SGLT2 inhibitors, sotagliflozin use increases the risks of ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum, and genital mycotic infections. DCN and DRM considered these risks and if a REMS was necessary to mitigate them.

Lexicon Pharmaceuticals, Inc. (Lexicon) submitted a New Drug Application (NDA) 216203 for sotagliflozin with the proposed indication to 1) reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) worsening heart failure regardless of left ventricular ejection fraction, and 2) 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) In late cycle minutes from March 16, 2023, the Agency expressed "that

(b) (4)

.[5] As such, the approved indication will be to reduce the risk of cardiovascular death 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.

The safety concerns associated with sotagliflozin use are similar to other marketed SGLT2 inhibitors, which use labeling to mitigate these risks. Proposed labeling for sotagliflozin includes similar language to convey the risks in warnings and precautions and clinical trial experience. Given the similarity of risks among SGLT2 inhibitors and length of time on the market of other SGLT2 inhibitors, we expect prescribers to be familiar with the risks. With the currently available data, additional risk mitigation measures beyond labeling are not necessary to ensure the benefits outweigh the risks of sotagliflozin.

9. Conclusion & Recommendations

Based on the available data, DRM and DCN agree that a REMS is not necessary to ensure the benefits of sotagliflozin outweigh the risks, which can be managed via labeling. Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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13. Lexicon Pharmaceuticals, Inc., Response to Clinical Information Request, December 15, 2022.
14. Lexicon Pharmaceuticals, Inc., Clinical Summary of Safety of Sotagliflozin, May 27, 2022.

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