



NDA 210934

COMPLETE RESPONSE

Lexicon Pharmaceuticals, Inc.
Attention: Thomas Noto
Senior Director, Regulatory Operations
2445 Technology Forest Blvd., 11th Floor
The Woodlands, Texas 77381

Dear Thomas Noto:

Please refer to your new drug application (NDA) (b) (4)

or sotagliflozin tablets.

We acknowledge receipt of your amendment dated (b) (4), which constituted a complete response to our (b) (4), action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

We have concluded that the data submitted are not sufficient to support a favorable benefit-risk assessment for sotagliflozin for the proposed indication as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus (T1D) and chronic kidney disease (CKD) in your proposed population of patients with estimated glomerular filtration rate (eGFR) of 45 to <60 ml/min/1.73m² or eGFR ≥60 ml/min/1.73m² and urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g or another population of patients with T1D and CKD defined by other parameters.

Diabetic ketoacidosis (DKA) was observed in the sotagliflozin dose groups compared to placebo in all three of the phase 3 clinical trials conducted in patients with T1D. During the review of the (b) (4), (original) NDA submission, the risk of DKA associated with the use of sotagliflozin in patients with T1D was estimated at one excess case of DKA for every 26 patients treated with sotagliflozin for one year. We concluded that the benefits associated with sotagliflozin in patients with T1D did not outweigh this DKA risk. The data in the (b) (4), resubmission do not support a conclusion that the risk of DKA associated with sotagliflozin is appreciably lower in the revised patient population and do not exclude the possibility that the risk may be higher in the revised patient population. In our review of your (b) (4), resubmission, we conclude the risk of DKA is unacceptably high given the comparatively modest benefits attributable to

improvements in glycemic control and given the uncertainties about non-glycemic benefits associated with sotagliflozin in patients with T1D and mild-to-moderate CKD.

We acknowledge that substantial evidence of effectiveness (SEE) for a glycemic control indication was demonstrated in the overall Tandem population, based on the primary analyses of the change-from-baseline (CFB) hemoglobin A1c (A1C) endpoint, during the review of the original NDA submission. We also acknowledge that the post hoc subgroup analyses of CFB A1C for patients with T1D and CKD were generally consistent with the primary analyses conducted in support of the original NDA submission. Overall, we agree the Tandem data demonstrate that the use of sotagliflozin results in modest but clinically meaningful reductions in A1C in patients with T1D and $\text{eGFR} \geq 60 \text{ ml/min/1.73m}^2$. It is unclear that efficacy has been established in patients with T1D and $\text{eGFR} < 60 \text{ ml/min/1.73m}^2$. We considered your rationale that improvements in A1C confer greater benefits to patients with T1D and mild-to-moderate CKD compared to patients with T1D without CKD. However, the evidence submitted to the NDA was insufficient to support a conclusion that the benefit of a modest A1C reduction outweighed the risk of DKA in the population(s) you proposed for your glycemic control indication.

We considered other benefits observed in the Tandem program. Sotagliflozin was consistently associated with a reduced risk of Level 2 hypoglycemia (events of blood glucose $< 54 \text{ mg/dL}$) in both the overall Tandem population and in subgroups of the Tandem population defined by various eGFR categories. We also acknowledge sotagliflozin was associated with small reductions in systolic blood pressure and body weight in both the overall Tandem population and in subgroups of the Tandem population defined by various eGFR categories. We also considered evidence for non-glycemic benefits based on new clinical data from a cardiovascular outcome trial (SCORED) conducted in subjects with type 2 diabetes mellitus (T2D), moderate-to-severe CKD, and other cardiovascular risk factors that were included in the (b) (4), resubmission. However, after considering these benefits in addition to the clinical benefit attributable to A1C reduction compared to the risk of DKA, we concluded that the totality of the data submitted did not support a favorable benefit-risk assessment in patients with T1D and $\text{eGFR} \geq 60 \text{ ml/min/1.73 m}^2$ and $\text{UACR} \geq 30 \text{ mg/g}$, the population meeting your proposed definition of CKD for which SEE has been demonstrated for a glycemic control indication.

Potential Path Forward

You have asserted that proper patient selection, monitoring, and appropriate risk mitigation strategies can mitigate the risk of DKA. However, evidence demonstrating that such strategies reduce the incidence and/or severity of DKA events below that which was observed in Tandem is lacking in your (b) (4), resubmission. Prospective clinical data demonstrating an acceptable risk of DKA with use of sotagliflozin would constitute one path forward. Additional evidence of effectiveness would not be necessary for population(s) where effectiveness has already been

established. Additional glycemic control data in patients with T1D would be necessary to support dosing recommendations in patients with T1D and eGFR <60 ml/min/1.73m².

To address the deficiencies in your application, you may demonstrate in a prospective, pragmatic open-label randomized clinical safety trial with a standard-of-care (i.e., not placebo controlled) active comparator arm that patient selection criteria and/or risk mitigation strategies adequately mitigate the risk of DKA. The safety data collection could be largely limited to rigorous collection of data associated with DKA events and other serious adverse events. We are open to discussing additional opportunities to streamline the trial design. For example, although a randomized trial with a standard-of-care comparator arm would have the advantage of estimating the additional DKA risk associated with use of sotagliflozin over background more reliably, we are open to the possibility that a single-arm study with an external control could provide evidence that the risk of DKA can be adequately mitigated. The ability of an externally controlled trial to support a conclusion that benefit/risk is favorable would depend on the magnitude of the DKA risk observed in study participants with T1D treated with sotagliflozin. We are also open to discussing whether any ongoing trials with sotagliflozin could be leveraged to demonstrate that patient selection criteria and/or risk mitigation strategies adequately mitigate DKA risk in patients with T1D. We recognize the unmet needs for patients with T1D and are committed to working with you. We strongly encourage you to request an End-of-Review meeting so that we may discuss a path forward.

Other potential paths forward include all options in our (b) (4), Complete Response Letter.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact

(b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

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/

(b) (4)

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