Testimony Before the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Regarding Sotagliflozin

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Public Citizen opposes approval of the New Drug Application (NDA) for sotagliflozin (Zynquista) as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus (T1D) and chronic kidney disease (CKD)[1] because there is a lack of substantial evidence demonstrating the effectiveness and safety of sotagliflozin in this population.

We are concerned that this NDA is based almost exclusively on post hoc analyses. These mainly include the post hoc analysis of sotagliflozin in the TANDEM clinical trials. These trials were conducted for the initial 2018 application for approval of sotagliflozin for all adults with type 1 diabetes.[2] In 2019, the FDA rejected this application because the modest benefits of the drug did not outweigh the unacceptable eightfold increased risk of life-threatening diabetic ketoacidosis (DKA) relative to placebo in the trials.[3] Importantly, only about 8.5% of subjects in the TANDEM trials even fit the definition of T1D and CKD in the revised application.[4]

The application also includes a post hoc analysis of a trial conducted in adults with type 2 diabetes (SCORED trial) that was also not designed to assess glycemic control.[5] No additional studies were conducted to assess the benefit and magnitude of harm of sotagliflozin in adults with CKD and T1D.

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[1] Food and Drug Administration. FDA briefing document. NDA# 210934. Drug name: sotagliflozin Applicant: Lexicon Pharmaceuticals, Inc. October 31, 2024. https://www.fda.gov/media/183160/download. Accessed October 31, 2024.
[2] *Id*. PDF p. 16, 21 and 102.
[3] Public Citizen. Letter to the FDA urging the agency not to approve the New Drug Application for sotagliflozin for treating type 1 diabetes. March 11, 2019. https://www.citizen.org/article/letter-to-the-fda-urging-the-agency-not-to-approve-the-new-drug-application-for-sotagliflozin-for-treating-type-1-diabetes/. Accessed October 31, 2024.
[4] Food and Drug Administration. FDA briefing document. NDA# 210934. Drug name: sotagliflozin Applicant: Lexicon Pharmaceuticals, Inc. October 31, 2024. https://www.fda.gov/media/183160/download. Accessed October 31, 2024.
[5] *Id.* PDF p. 24.

The sponsor seems to have based its decision to limit the population in the NDA to patients with T1D and CKD on the assumptions that "similar improvements in glycemic control confer greater benefits to patients with T1D and CKD"[6] as compared to patients with T1D alone and that "the estimates of DKA risk in the overall TANDEM population are transportable to the revised population of patients."[7] However, the available data do not substantiate these claims.

For example, we agree with the FDA that although the post hoc analyses "do not support definitive conclusions about the magnitude of treatment effect,"[8] it appears that the treatment effect on A1C was smaller for some CKD patients than the treatment effect observed in the overall population. Except for a potential risk reduction in hypoglycemia, no additional benefits were convincingly demonstrated.

More concerningly, the risk of DKA in the revised population appears to be similar to or possibly even higher than in the overall population, although again, due to the small number of observed events in the revised population, no meaningful conclusion can be drawn.[9] Moreover, not enough is known about the potential effects of sotagliflozin on the DKA risk in CKD patients.[10] Public Citizen is very concerned that the risk of DKA events will be even higher if the drug is approved and used in clinical practice.[11]

We therefore urge the advisory committee to vote "No" on the voting question and strongly recommend that the FDA not approve sotagliflozin for type 1 diabetes patients with chronic kidney disease.

[6] *Id*. PDF p. 16.
[7] *Id*. PDF p. 41.
[8] *Id.* PDF p. 30, 49 and 50-52.
[9] *Id*. PDF p. 43-44, 52-53.
[10] *Id*. PDF p. 47.
[11] Public Citizen. Letter to the FDA urging the agency not to approve the New Drug Application for sotagliflozin for treating type 1 diabetes. March 11, 2019. https://www.citizen.org/article/letter-to-the-fda-urging-the-agency-not-to-approve-the-new-drug-application-for-sotagliflozin-for-treating-type-1-diabetes/. Accessed October 31, 2024.