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March 11, 2019

Scott Gottlieb, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: New drug application for sotagliflozin for treatment of type 1 diabetes mellitus

Dear Commissioner Gottlieb, Dr. Woodcock, and Dr. Yanoff:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to strongly urge the Food and Drug Administration (FDA) not to approve the new drug application (NDA) submitted by Sanofi for sotagliflozin (ZYNQUISTA) for use as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus (T1DM). Sotagliflozin was the subject of the January 17, 2019, meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC).

Public Citizen strongly opposes approval of sotagliflozin because the data from the phase 3 clinical trials presented in the NDA show that the drug causes an unacceptable eight-fold increased risk of life-threatening diabetic ketoacidosis (DKA), usually requiring hospitalization, in subjects with T1DM given the drug, compared with those given a placebo. In addition,

Sanofi's choice of what the FDA considers a highly questionable composite primary endpoint for the phase 3 clinical trials raises serious questions about the overall benefit of the drug. This composite endpoint consisted of a lowering of blood sugar as measured by hemoglobin A1c (HbA1c) to less than 7%, combined with the absence of both DKA and severe hypoglycemia. In the briefing package for the January 17, 2019 EMDAC meeting, the FDA stated that "This endpoint attempts to incorporate benefit and risk into a single composite, but we have concerns about the clinical significance of the chosen composite…such [benefit-risk] assessments must start with a clinically meaningful way to frame both benefits and risks."[1]

Other key information from the FDA briefing materials for the EMDAC meeting include the following:

- "Sotagliflozin was associated with an approximately 8-fold increase in DKA risk vs. placebo (95% CI: [3.1, 19.9]). The estimated number needed to harm (NNH) was approximately 26 patient-years of exposure to sotagliflozin to observe 1 additional DKA event (95% CI: [20.1, 38.5])."

- "Subgroup analyses showed a consistently elevated DKA risk associated with sotagliflozin, with estimated hazard ratios ranging from 4 to 11, and NNH ranging from 11 to 37."

- The rate of adjudicated DKA cases in the three trials:
  -Placebo: 5 cases/1229 patients=0.4%
  -Sotagliflozin: 56 cases/1748 patients=3.2%[2]

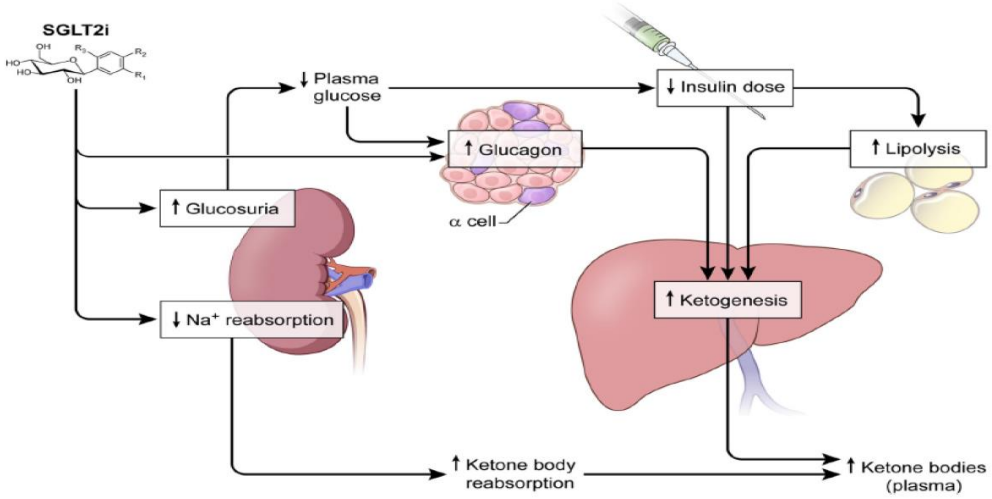
The FDA presentation at the January 17, 2019, EMDAC meeting included the following slide from a 2015 publication outlining the multiple known mechanisms whereby SGLT2 inhibitors can cause DKA:[3]

[1] Food and Drug Administration. FDA briefing document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting. January 17, 2019. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM629485.pdf. Accessed March 10, 2019. PDF p. 11.

[2] *Ibid*. PDF pp. 24-35 and 71.

[3] Food and Drug Administration. Slides for FDA presentations at the January 17, 2019, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM629782.pdf. Accessed March 10, 2019. PDF p. 56.

Pathophysiology of SGLT2-associated DKA



DKA: Diabetic ketoacidosis
SGLT2: sodium glucose co-transporter 2

Taylor, et al. SGLT2 Inhibitors May Predispose to Ketoacidosis. *Journal of Clinical Endocrinology and Metabolism.* 2015, 100(8):2949-2853

According to the minutes of the EMDAC meeting, some committee "members were concerned, citing the number of observed DKA events relative to placebo in the phase 3 studies and the probability that the risk could be even higher in the real-world setting outside the confines of a clinical trial. The committee members noted that there was no evidence the risk mitigation strategy proposed by the applicant works."[4]

A paper entitled "International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors" that was published online on February 6, 2019, almost three weeks after the EMDAC meeting, was authored by international clinical investigators, including several who spoke during the open public hearing of the advisory committee meeting. The paper's stated purpose was the following:

> "Strategies must be developed and disseminated to the medical community to mitigate the associated DKA risk. This consensus report reviews current data regarding SGLT-inhibitor use and provides recommendations to enhance the safety of SGLT-inhibitors in people with type 1 diabetes."[5]

[4] Food and Drug Administration. Minutes of the January 17, 2019, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM632454.pdf. Accessed March 10, 2019. PDF p. 5.

[5] Danne T, Garg S, Peters AL, et al. International consensus on risk management of diabetic ketoacidosis in patients with type 1 diabetes treated with sodium-glucose cotransporter (SGLT) inhibitors. *Diabetes Care*. 2019 Feb 6. pii: dc182316. doi: 10.2337/dc18-2316. [Epub ahead of print].

It is notable that many of these internationally agreed-upon recommendations are quite similar to, but not as rigorous as, those used in one of the published phase 3 clinical trials (Garg et al) upon which the NDA for sotagliflozin is based, not surprising since many the authors of the international consensus paper were also investigators in that trial.[6]

For example, the protocol for the Garg et al trial detailed monitoring of ketones — an essential factor in the diagnosis of DKA — in trial subjects as follows:

> "At every clinic visit blood BHB [betahydroxybutyrate, a ketone] (central laboratory and point-of-care) testing will be conducted. At visits where UA is performed, the evaluation will include urine ketone determination by dipstick."[7]

Many of the elements of the risk mitigation strategy proposed by Sanofi likewise are quite similar to those in the internationally agreed-upon recommendations mentioned above. The FDA's criticism concerning Sanofi's risk mitigation strategy was that "Mitigation strategies to reduce the risk of DKA post-marketing have not been tested in premarket studies."[8] It is likely, if not certain, that because of the more rigorous DKA prevention strategies employed in the clinical trial, the eight-fold increased risk of DKA seen in the phase 3 clinical trials represents the lowest achievable risk because of such increased scrutiny of the subjects.

The reasonable concern expressed by some EMDAC members that "the risk [of DKA with sotagliflozin use in patients with T1DM] could be even higher in the real-world setting outside the confines of a clinical trial"[9] is supported by the Sentinel data presented by the FDA at the advisory committee meeting. For this analysis, the FDA utilized its real-world Sentinel data to calculate the risk of DKA in T1DM patients who had been prescribed previously approved SGLT Inhibitors off label, since they are only approved by the FDA for treatment of type 2 diabetes. This instructive analysis by the FDA of the Sentinel data, presented at the January 17, 2019, EMDAC meeting, found that in patients with T1DM who had received one of the previously approved SGLT2 inhibitors off-label, the risk of DKA was actually 1.83 times higher in a properly narrowly defined group of T1DM patients for all age groups than the risk for subjects in the sotagliflozin phase 3 clinical trials.[10]

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[6] Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med* 2017;377(24):2237-2348.

[7] Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med* 2017;377(24):2237-2348. Supplementary appendix, PDF p. 29.

[8] Food and Drug Administration. Slides for FDA presentations at the January 17, 2019, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM629782.pdf. Accessed March 10, 2019. PDF p. 116.

[9] Food and Drug Administration. Minutes of the January 17, 2019, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM632454.pdf. Accessed March 10, 2019. PDF p. 5.

[10] Food and Drug Administration. FDA briefing document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting. January 17, 2019.

In conclusion, the "gold standard" for the lower limit of the risk of DKA with sotagliflozin, if the drug is inexplicably approved, will likely be the eight-fold increased risk of DKA found in the phase 3 clinical trials. This extraordinarily increased risk of life-threatening DKA, which usually requires hospitalization, is not only unacceptable but would most likely represent the highest serious pre-approval risk of any diabetes treatment ever approved by the FDA. For those patients in the real world, the risk is certain to be even higher.

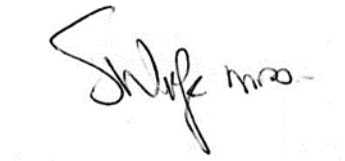
During the open public hearing at the January 17, 2019, EMDAC meeting, the comments were dominated by speakers with sotagliflozin-positive anecdotes but lacked any objective evidence of benefit beyond the relatively small changes in HbA1c levels. One advisory committee member remarked on the lack of any speaker who had personally suffered DKA and could relate the impact of this serious adverse drug reaction.[11] Those advisory committee members opposing approval noted that "although innovative therapies for patients with type 1 diabetes are needed, there is a concerning risk of DKA, and the applicant did not demonstrate sufficient data to support benefit beyond modest reductions in HbA1c, and has not shown data supporting ketone monitoring or other risk mitigation strategies to be effective in mitigating DKA risk."[12]

Patients with T1DM should not be exposed to a drug with documented harm clearly exceeding benefit. If inexcusably approved by the FDA, sotagliflozin will almost certainly be withdrawn from the market, but only after hundreds or more T1DM patients suffer, and some die from, DKA.

Public Citizen therefore urges the FDA to reject the NDA for sotagliflozin.

Thank you for considering our comments on this important matter.

Sincerely,



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

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https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM629485.pdf. Accessed March 10, 2019. PDF p. 121.

[11] Food and Drug Administration. Webcast of the January 17, 2019, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, afternoon break to end of meeting. https://collaboration.fda.gov/pa9l91i8d1ht/?OWASP_CSRFTOKEN=38224d0d6438a20c814f129619a9dafdde69e1c71c8c1cbba0d67d3f12fcb919. Accessed March 10, 2019.

[12] Food and Drug Administration. Minutes of the January 17, 2019, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM632454.pdf. Accessed March 10, 2019. PDF p. 7.