Sidney M. Wolfe, MD
Michael A. Carome, MD
Public Citizen
1600 20th Street, NW
Washington, D.C. 20009

May 19, 2023

Re: Docket No. FDA-2020-P-1611

Dear Drs. Wolfe and Carome:

This letter responds to your citizen petition, which was received on June 24, 2020 (Petition). In your Petition, you request that the Food and Drug Administration (FDA, Agency, or we) immediately take action to require a boxed warning for all sodium-glucose co-transporter 2 (SGLT2) inhibitor drugs, including all combination products containing these drugs, contraindicating their use in patients with type 1 diabetes mellitus.

The Petition requests that FDA "immediately require that the following changes be made to the drug product labeling for all FDA-approved SGLT2 inhibitor drugs" and proposes sample wording (Petition at 2–4, suggested language excluded):

1) "The addition of a boxed warning stating that use of the drug in patients with type 1 diabetes is contraindicated and briefly reviewing the strong evidence from randomized clinical trials that support this contraindication."

2) "The addition of a new first bullet to the CONTRAINDICATIONS section indicating that the use of the drug in patients with type 1 diabetes is contraindicated."

3) "In the WARNINGS AND PRECAUTIONS section under the subheading "Ketoacidosis," the addition of a warning stating that use of the drug in patients with type 1 diabetes is contraindicated because of the increased risk of DKA [diabetic ketoacidosis] and briefly reviewing the strong evidence for this contraindication."

4) "The addition of a statement to the beginning of the patient Medication Guide indicating that the use of the drug in patients with type 1 diabetes is contraindicated."

5) "Corresponding changes to "Limitation of Use" statements in the INDICATIONS AND USAGE section."

We have carefully considered your Petition and other relevant data available to the Agency. Based on our review of these materials, and for the reasons stated below, your Petition is denied.

I. BACKGROUND

A. Prescription Drug Product Labeling

1. Overview of Relevant Statutory and Regulatory Requirements

FDA-approved drug product labeling summarizes the essential information needed for the safe and effective use of the drug and reflects FDA's finding on the safety and effectiveness of the drug under the labeled conditions of use.[1] The primary purpose of FDA-approved labeling for prescription drug products is to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions, thereby enhancing the safe and effective use of prescription drug products and reducing the likelihood of medication errors. Prescription drug product labeling is directed to health care practitioners but may also include additional FDA-approved labeling directed at the patient or caregiver (commonly referred to as *patient labeling*).

2. Certain Labeling Content Requirements and Related Agency Guidance

FDA regulations govern the content and format of prescription drug product labeling.[2] The regulations are intended to organize labeling information to more effectively communicate to health care professionals the "information necessary for the safe and effective use of prescription drugs."[3]

Labeling regulations are further discussed in FDA guidances about specific topics related to the content and format of prescription drug product labeling. When finalized, guidances describe the Agency's current thinking on those topics.[4] Currently available labeling-related guidances may address a single section of labeling, multiple sections, or a discrete topic on prescription drug product labeling.

The statutory and regulatory requirements for the two main sections of labeling for which revisions are requested in the Petition are discussed briefly below. Other requested revisions are addressed in section II.B.3, Requests for Other Labeling Changes.

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[1] See 21 CFR 201.56(a).

[2] See, for example, 21 CFR 201.56 and 201.57; see also 21 CFR 201.100(c).

[3] The final rule, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (physician labeling rule), published January 24, 2006 (71 FR 3922 at 3928). For the content and format requirements for the labeling of older prescription drug products that are not subject to the labeling requirements in 21 CFR 201.56 and 201.57, see 21 CFR 201.80. The specific labeling requirements for older drug products differ in certain respects and generally are not referenced in this response.

[4] Labeling guidances are available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. FDA's guidance documents generally do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The CONTRAINDICATIONS section of labeling must describe any situations in which the drug should not be used because the risk of use "clearly outweighs any possible therapeutic benefit."[5] Those situations include use of the drug in patients "who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable."[6]

FDA may require a boxed warning in labeling for certain contraindications or serious warnings, particularly those that may lead to death or serious injury, because this information is especially important for a health care practitioner to consider in assessing the risks and benefits of a drug.[7] The BOXED WARNING section must briefly explain the risk and then refer to the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section of labeling, where the risk is explained in more detail.[8,9]

B. Diabetes Mellitus and SGLT2 Inhibitor Drugs

1. Type 1 and Type 2 Diabetes Mellitus

Diabetes mellitus occurs when the level of glucose in the blood is elevated. In patients with diabetes mellitus, the hormone insulin, which helps remove glucose from the blood, is either present in inadequate amounts or is not used efficiently by the body. There are two main types of diabetes mellitus: type 1 and type 2.

Type 1 diabetes mellitus (T1DM) is a chronic serious medical condition resulting from autoimmune destruction of pancreatic beta cells leading to insulin deficiency and a state of hyperglycemia. Because of the state of insulin deficiency in these patients, the mainstay of treatment for T1DM is exogenous insulin. Other than insulin, treatment options for T1DM are limited, with only one other drug currently approved to improve glycemic control (as an adjunct to insulin) in patients with T1DM.[10]

Type 2 diabetes mellitus (T2DM) occurs when the body does not make or use insulin well. It is usually diagnosed in adults, and risk factors include being overweight or obese, being physically inactive, having a family history of diabetes, or having a history of gestational diabetes. In

[5] 21 CFR 201.57(c)(5).

[6] *Ibid.* This concept is explained further in the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011) (Warnings Guidance), at 8. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] See 21 CFR 201.57(c)(1).

[8] *Id.*

[9] See the Warnings Guidance at 11.

[10] Symlin (pramlintide acetate) injection, new drug application 021332, originally approved March 16, 2005.

addition to lifestyle modifications (e.g., diet, exercise), many patients with T2DM need to take glucose-lowering drugs, which may be taken orally or by injection (e.g., insulin).

2. SGLT2 Inhibitor Drugs

SGLT2, a protein expressed in the proximal tubules of the kidney, is responsible for the majority of the reabsorption of filtered glucose back into the plasma. SGLT2 inhibitor drugs lower plasma glucose by reducing glucose reabsorption and increasing glucose excretion in the urine.

There are currently five SGLT2 inhibitor drugs approved by FDA in the United States. They are marketed as either single-ingredient drugs or fixed-combination drug products in which the SGLT2 inhibitor drug is combined with one or two other diabetes drugs from other pharmacological classes.[11] All SGLT2 inhibitor drug products carry a common indication in their labeling, which states that each is indicated "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." No SGLT2 inhibitor drug is approved to improve glycemic control in patients with T1DM.

In addition, three of the five marketed SGLT2 inhibitor drugs are also approved for indications to reduce the risk of certain cardiovascular and renal adverse outcomes. Some of these additional indications are specific to patients with both T2DM and other conditions or risk factors, and other indications are for conditions regardless of the presence or absence of concomitant diabetes.

C. Diabetic Ketoacidosis

An absence of insulin results in diabetic ketoacidosis (DKA),[12] a life-threatening condition characterized by hyperglycemia (blood glucose greater than 250 milligrams (mg)/deciliter (dL)), metabolic acidosis, and increases in total body ketone concentration. Treatment of DKA necessitates correction of dehydration, hyperglycemia, and electrolyte imbalances; identification and management of comorbid precipitating events; and most importantly, frequent monitoring of patients. Most patients who develop DKA have T1DM, but patients with T2DM are also at risk, especially during catabolic stressors such as trauma, surgery, or infection. Patients with diabetes are advised to monitor blood glucose and ketone levels at home, potentially facilitating early recognition of impending DKA and appropriate interventions.[13]

[11] Currently approved fixed-combination drug products containing an SGLT2 inhibitor drug combine it with metformin, a dipeptidyl peptidase-4 inhibitor (i.e., linagliptin, saxagliptin, or sitagliptin), or both.

[12] Kitabchi AE, Umpierrez GE, Miles JM, and Fisher JN, 2009, Hyperglycemic Crises in Adult Patients With Diabetes, Diabetes Care, 32(7):1335–43, doi: 10.2337/dc09-9032.

[13] *Ibid.*

Among patients who develop DKA while taking SGLT2 inhibitor drugs, blood glucose levels may not be elevated, with levels below 250 mg/dL (i.e., euglycemic DKA).[14] Atypical presentations such as these may lead to delays in recognizing and treating cases of DKA.

D. Current Labeling

Currently approved labeling for SGLT2 inhibitor drug products includes information on the risk of ketoacidosis in several sections. With minor differences for certain product-specific information, the labeling for each of these drug products includes language similar to what appears below.

In the INDICATIONS AND USAGE section:

> Limitations of Use
> [Drug name] is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.X)]*.

In the WARNINGS AND PRECAUTIONS section:

> **5.1 [or 5.2] Ketoacidosis**
> Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus who received SGLT2 inhibitors, including [Drug name]. Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. [Drug name] is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.
>
> Patients treated with [Drug name] who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with [Drug name] may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, [Drug name] should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.
>
> In many of the reported cases, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included

[14] Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, and Hirsch IB, 2015, Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition, Diabetes Care, 38(9):1687–93, doi: 10.2337/dc15-0843.

> nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified. Before initiating [Drug name], consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.
>
> For patients who undergo scheduled surgery, consider temporarily discontinuing [Drug name] for at least [X] days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.
>
> Consider monitoring for ketoacidosis and temporarily discontinuing [Drug name] in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting [Drug name].
>
> Educate patients on the signs and symptoms of ketoacidosis, and instruct patients to discontinue [Drug name] and seek medical attention immediately if signs and symptoms occur.

In the PATIENT COUNSELING INFORMATION section:[15]

> Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of [Drug name], sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue [Drug name] and seek medical attention immediately *[see Warnings and Precautions (5.X)]*.

In the Medication Guide, a document written for the patient (or caregiver) that is part of FDA-approved labeling (emphasis original):

> **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes treated with medicines like [Drug name] or in people with type 2 diabetes during treatment with [Drug name]**. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with medicines like [Drug name]. Ketoacidosis is a serious condition, which needs to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with [Drug name] even if your blood sugar is less than 250 mg/dL. Stop**

[15] We note that the Petition did not request any changes to the PATIENT COUNSELING INFORMATION section of labeling. It is included here for completeness on current labeling content related to ketoacidosis.

taking [Drug name] and call your healthcare provider right away or go to the nearest hospital emergency room if you have any of the following symptoms:

- nausea
- vomiting
- stomach-area (abdominal) pain
- tiredness
- trouble breathing

If you get any of these symptoms during treatment with [Drug name], if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.

II. DISCUSSION

A. Review of Available Data

FDA has reviewed the references submitted in the Petition, as well as other information available to the Agency, and we have concluded that they do not support the addition of a contraindication to use of SGLT2 inhibitor drug products for T1DM.

The Petition references several publications on the use of SGLT2 inhibitor drugs for glycemic control in patients with T1DM, including eight phase 3 clinical trials (Petition at 9–10). FDA largely agrees with the findings as described in these individual trial publications based on our scientific reviews of the same data as part of individual drug applications seeking approval for use to improve glycemic control in patients with T1DM. The Petition also references a published meta-analysis,[16] which encompasses these eight trials plus two small phase 2 trials (Petition at 11). However, we find the conclusions in the meta-analysis to be problematic because results from the two phase 2 trials included in the analysis were published in nonpeer-reviewed publications for which there is minimal study-specific information available.[17, 18] Furthermore, DKA was adjudicated differently in each of the trials, and the meta-analysis did not account for these differences in the definition of a DKA event. Therefore, the conclusions of the meta-analysis may be unreliable because of the lack of a standardized definition of what constituted a DKA event.

The Petition also cites findings from a published analysis of data from FDA's Sentinel System in support of its request for a contraindication to use of SGLT2 inhibitor drugs in patients with

[16] Lu J, Tang L, Meng H, Zhao J, and Liang Y, 2019, Effects of Sodium-Glucose Cotransporter (SGLT) Inhibitors in Addition to Insulin Therapy on Glucose Control and Safety Outcomes in Adults With Type 1 Diabetes: A Meta-analysis of Randomized Controlled Trials, Diabetes Metab Res Rev, 35(7):e3169, doi: 10.1002/dmrr.3169.

[17] Bode B, Banks P, Sawhney S, and Strumph P, 2017, Efficacy and Safety of Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct to Insulin in Young Adults With Poorly Controlled Type 1 Diabetes (JDRF Study; NCT02383940). In: Pediatric Diabetes, Volume 18: Abstracts for the 43rd Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD), October 18–21, 2017, Innsbruck, Austria. Abstract O19 is available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/pedi.12587.

[18] Baker C, Wason S, Banks P, Sawhney S, and Strumph P, 2017, A 12-Week Dose-Ranging Study of Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes (inTandem4), Diabetologia, 60(S1):S409.

T1DM.[19] Specifically, the Petition includes the reported rates of DKA in patients (with either T1DM or T2DM) who had recently begun taking SGLT2 inhibitor drugs (Petition at 13-14). Although we acknowledge that the DKA rates from this analysis noted in the Petition reflect those reported in the published paper, we note that these data came from a descriptive study that was designed to estimate the rates of DKA in patients with T1DM and T2DM exposed to SGLT2 inhibitor drugs but not designed to test formally the differences in rates between these two groups.

We do not agree, however, with the Petition's characterization of data from the FDA Adverse Event Reporting System (FAERS) (Petition at 12-13). Specifically, we disagree with the number and description of the seriousness of the additional cases of DKA the Petition identifies beyond those compiled by FDA and shared publicly at the meeting of the Endocrinologic and Metabolic Drugs Advisory Committee on January 17, 2019 (at which the new drug application 210934 for sotagliflozin, a dual SGLT1/SGLT2 inhibitor drug, was discussed).[20] The Petition does not indicate whether you reviewed individual case narratives to exclude duplicate reports or to establish an association between use of the SGLT2 inhibitor drug and the DKA event, both of which FDA did as part of its 2019 review. Furthermore, as noted in FDA's briefing document[21] for the 2019 meeting, a limitation of FAERS data is that there is no certainty of causality such that a reported event occurred because of use of a product. Adverse event report submission to FAERS does not require that a causal relationship between a product and event be proven, and case narratives can often help determine whether the adverse event of interest is probably, possibly, or unlikely related to the product.

Accordingly, we have determined that the references submitted in the Petition, and other information reviewed by the Agency, do not further contribute to the current understanding of the DKA risk in patients with T1DM using SGLT2 inhibitor drugs to improve glycemic control.

B. Requested Labeling Changes

In the Petition, you request changes to several sections of labeling, each based on the assertion that a contraindication to the use of SGLT2 inhibitor drugs for T1DM is warranted. For ease of reading, we will first discuss the request for a contraindication and follow with your requests for other corresponding labeling changes that would be based on that contraindication.

1. Request to Add a Contraindication

Based on our review, we disagree that a contraindication to the use of SGLT2 inhibitor drugs for T1DM is warranted. Although SGLT2 inhibitor drugs are not indicated for glycemic control in

[19] Hampp C, Swain RS, Horgan C, Dee E, Qiang Y, Dutcher SK, Petrone A, Tilney RC, Maro JC, and Panozzo CA, 2020, Use of Sodium-Glucose Cotransporter 2 Inhibitors in Patients With Type 1 Diabetes and Rates of Diabetic Ketoacidosis, Diabetes Care, 43(1):90-7, doi: 10.2337/dc19-1481.

[20] For meeting materials, see https://wayback.archive-it.org/7993/20201224220030/https://www.fda.gov/advisory-committees/advisory-committee-calendar/january-17-2019-meeting-endocrinologic-and-metabolic-drugs-advisory-committee-meeting-announcement.

[21] *Ibid.*

patients with T1DM, it does not follow that the drugs should be contraindicated for such use in patients with T1DM; the absence of an approved indication in a given population or condition does not automatically necessitate a contraindication in that group.

We believe that the WARNINGS AND PRECAUTIONS section remains the appropriate primary location in labeling to communicate the risk of DKA, particularly as associated with use of SGLT2 inhibitor drugs by patients with T1DM. Per regulation, the WARNINGS AND PRECAUTIONS section must describe "clinically significant adverse reactions," other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur when "reasonable evidence of a causal association" between the drug and such hazards exists.[22]

FDA regulations further state that, in the WARNINGS AND PRECAUTIONS section, a "specific warning relating to a use not provided for under the INDICATIONS AND USAGE section may be required by FDA in accordance with sections 201(n) [21 U.S.C. 331(n)] and 502(a) [21 U.S.C. 352(a)] of the [Federal Food, Drug, and Cosmetic Act] if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard."[23] Accordingly, information about the risk of DKA when SGLT2 inhibitor drugs are used for glycemic control in patients with T1DM — a use not provided for under the INDICATIONS AND USAGE section — is included in the WARNINGS AND PRECAUTIONS section. A risk related to an unapproved use is generally not included in the CONTRAINDICATIONS section, especially when information on said risk is already appropriately described in the WARNINGS AND PRECAUTIONS section (and sometimes also discussed elsewhere in labeling, e.g., under the Limitations of Use heading in the INDICATIONS AND USAGE section. See section II.B.3, Requests for Other Labeling Changes.).

After a review of the references submitted in the Petition and other data available to the Agency, and for the reasons cited above, your request to add a contraindication to use of SGLT2 inhibitor drugs for T1DM is denied.

2. Request to Add a Boxed Warning

In the Petition, you request that a boxed warning be added to the labeling for SGLT2 inhibitor drug products that further emphasizes your proposed new contraindication and that briefly reviews the supportive evidence. FDA does not agree that a boxed warning is warranted.

[22] 21 CFR 201.57(c)(6)(i).

[23] *Ibid.*

Since 2015, FDA has required safety labeling changes[24] addressing the risk of DKA for SGLT2 inhibitor drugs three times, most recently in 2020.[25] In each instance, FDA determined that the WARNINGS AND PRECAUTIONS section, with revisions, was the appropriate location in labeling for the primary discussion of the risk of DKA to ensure that the labeling contained the essential information needed for the safe and effective use of SGLT2 inhibitor drug products. FDA's most recent review, performed in response to this Petition, has identified no new information that would warrant a change in this approach.

Because we disagree that a contraindication is warranted and are denying the request to add one, and for the reasons cited above, we are also denying your request for the addition of a boxed warning.

3. Requests for Other Labeling Changes

The Petition requests that information on the proposed contraindication be added under the existing Limitations of Use heading in the INDICATIONS AND USAGE section of labeling. Because we are denying the request to add a contraindication to use of SGLT2 inhibitor drug products for T1DM, we are also denying adding information on such a contraindication to the INDICATIONS AND USAGE section. For the same reason, we are also denying your requests to incorporate information on the proposed contraindication into the WARNINGS AND PRECAUTIONS section of labeling and the Medication Guide patient labeling document.

III. CONCLUSION

For the reasons set forth above, your requests for labeling changes for SGLT2 inhibitor drug products are denied. As with all FDA-approved drug products, we will continue to monitor and review available safety information related to SGLT2 inhibitor drugs throughout the product life cycles and will take further action if we determine it is appropriate to do so.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2023.05.19 11:45:43 -04'00'

Patrizia Cavazzoni, MD
Director
Center for Drug Evaluation and Research

[24] Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require certain holders of approved applications for prescription drug products to make safety labeling changes if the Agency becomes aware of "new safety information" that FDA believes should be included in the drug's labeling.

[25] Revised labeling for SGLT2 inhibitor drug products under this safety labeling change was approved on January 24, 2020.