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## Citizen Petition

Date: June 24, 2020

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and Public Citizen's Health Research Group, the undersigned submit this petition under Sections 502 and 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §§ 352 and 355(o)(4)) and under Food and Drug Administration (FDA) regulations at 21 C.F.R. §§ 10.30, 201.56, 201.57(c)(1) and 201.57(c)(5) to request that the Commissioner of Food and Drugs immediately take the actions requested below to require a boxed warning for all sodium-glucose cotransporter-2 (SGLT2) inhibitor drugs contraindicating their use in patients with type 1 diabetes mellitus (hereafter, diabetes).

There is irrefutable evidence from multiple randomized clinical trials that the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin — which are approved for treatment of adults with type 2 diabetes but not type 1 diabetes (and in the case of dapagliflozin, also for treatment of adults with heart failure and a reduced cardiac ejection fraction) — cause a significant increase in the incidence of life-threatening diabetic ketoacidosis (DKA) when administered to patients with type 1 diabetes. The most recently approved SGLT2 inhibitor, ertugliflozin — which also is approved only for treating adults with type 2 diabetes mellitus — has not been studied for use in patients with type 1 diabetes, but the FDA considers ertugliflozin's risk of DKA for such patients to be similar to that of patients taking canagliflozin, dapagliflozin, and empagliflozin, and product labeling for ertugliflozin includes warnings about DKA that are identical to those found in the product labeling for the three other SGLT2 inhibitors.

The current dangerous off-label prescribing of these drugs to patients with type 1 diabetes, which has been well documented by the FDA, is enabled by the dangerous incompleteness and submerged prominence of the warnings about the risk of DKA in the drugs' current product labeling. This includes the failure to acknowledge anywhere in the labels the extensive evidence from randomized, placebo-controlled trials demonstrating that SGLT2 inhibitors cause a marked increase in the risk of DKA when used to treat patients with type 1 diabetes. As a result, there have been 374 new cases of DKA associated with use of SGLT2 inhibitors in patients with type 1 diabetes that have been reported to the FDA during the more than four years since the weak, incomplete warning of any risk of ketoacidosis was first added to the product labeling for canagliflozin, dapagliflozin, and empagliflozin in late 2015. The number of such preventable DKA cases likely would be greatly diminished if a prominent boxed warning were added at the beginning of the product labeling for all SGLT2 inhibitors, not merely stating — as their labeling

has stated since approval — that these drugs are not approved or recommended for type 1 diabetes but that they are contraindicated for these patients because of their greatly increased susceptibility to SGLT2-induced DKA.

Importantly, during 2019, the FDA rejected the efforts by two companies to gain additional approval of dapagliflozin and empagliflozin for treatment of patients with type 1 diabetes, concluding that the drugs' benefits are greatly outweighed by the increased risk of DKA in such patients. By 2015, the first clinical trial of canagliflozin in patients with type 1 diabetes had been completed, but because of the large increase in DKA incidence in these patients, the company apparently decided not to apply for approval for this indication. A dual SGLT1/SGLT2 inhibitor, sotagliflozin, never approved for type 2 diabetes, also was rejected in 2019 by the FDA for treatment of type 1 diabetes because it similarly caused a large increase in DKA incidence without offsetting benefits.

Just as the FDA previously has concluded that for certain drugs a boxed warning contraindicating the use of those drugs in patients with certain diseases or conditions is necessary, all SGLT2 inhibitors should be contraindicated for patients with type 1 diabetes. A boxed warning contraindicating use of all SGLT2 inhibitors for type 1 diabetes and briefly reviewing the strong evidence for this warning is likely to reduce the ongoing but preventable life-threatening toll of SGLT2 inhibitor-induced DKA in many hundreds of patients with type 1 diabetes. The basis for this boxed contraindication warning can be elaborated upon further in the contraindication section and warnings and precautions section of the label and included in the patient Medication Guide.

## **A. ACTIONS REQUESTED**

Immediately require that the following changes be made to the product labeling for all FDA-approved SGLT2 inhibitors, including all combination products containing these drugs:<sup>1</sup>

- (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. We suggest the following wording for the requested boxed warning:

**WARNING: CONTRAINDICATION FOR TYPE 1 DIABETES  
MELLITUS**

**Increased Risk of Diabetic Ketoacidosis (DKA) in Patients with Type 1  
Diabetes Mellitus Who Use [Name of Drug]: Use of [name of drug] in**

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<sup>1</sup> SGLT2 inhibitors currently approved by the FDA include the following: canagliflozin (INVOKANA); canagliflozin and metformin (INVOKAMET, INVOKAMET XR); dapagliflozin (FARXIGA); dapagliflozin and metformin (XIGDUO XR); dapagliflozin and saxagliptin (QTERN); dapagliflozin, metformin, and saxagliptin (QTERNMET); empagliflozin (JARDIANCE); empagliflozin and metformin (SYNJARDY, SYNDARDY XR); empagliflozin and linagliptin (GLYXAMBI); empagliflozin, linagliptin, and metformin (TRIJARDY XR); ertugliflozin (STEGLATRO); ertugliflozin and metformin (SEGLUROMET); and ertugliflozin and sitagliptin (STEGLUJAN).

**patients with type 1 diabetes mellitus, for whom the drug is not approved, is contraindicated. In eight large randomized, placebo-controlled, double-blind clinical trials that each assessed the safety and efficacy of one of three SGLT2 inhibitors or one dual SGLT1/SGLT2 inhibitor as add-on therapy to insulin for patients with type 1 diabetes, the collective number of subjects who developed DKA was 141 (3.3%) of 4,317 subjects treated with an SGLT2 or dual SGLT1/SGLT2 inhibitor and 16 (0.7%) of 2,362 placebo-treated subjects. A published meta-analysis of these eight clinical trials and two additional small unpublished trials found that the risk of DKA in the SGLT2 or dual SGLT1/SGLT2 inhibitor-treated subjects was significantly increased compared with placebo-treated subjects (relative risk 3.11; 95% CI, 2.11-4.58) [see Warnings and Precautions].**

(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. We suggest the following wording for the new bullet:

- Use of [name of drug] in patients with type 1 diabetes mellitus, for whom the drug is not approved, is contraindicated. [see Warnings and Precautions]

(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 and briefly reviewing the strong evidence for this contraindication. We suggest the following wording for the requested warning be added at the beginning of the ketoacidosis warning subsection:

Use of [name of drug] in patients with type 1 diabetes mellitus, for whom the drug is not approved, is contraindicated because of the marked increase in the risk of DKA. In eight large randomized, placebo-controlled, double-blind clinical trials that each assessed the safety and efficacy of one of three SGLT2 inhibitors or one dual SGLT1/SGLT2 inhibitor as add-on therapy to insulin for patients with type 1 diabetes, the collective number of subjects who developed DKA was 141 (3.3%) of 4,317 subjects treated with an SGLT2 or dual SGLT1/SGLT2 inhibitor and 16 (0.7%) of 2,362 placebo-treated subjects. A published meta-analysis of these eight clinical trials and two additional small unpublished trials found that the risk of DKA in the SGLT2 or dual SGLT1/SGLT2 inhibitor-treated subjects was significantly increased compared with placebo-treated subjects (relative risk 3.11; 95% CI, 2.11-4.58).

Additional evidence for this life-threatening risk comes from an FDA-conducted real-world study of Sentinel System data, which found a DKA rate of 7.3 events per 100 person-years in patients meeting narrowly defined criteria for type 1 diabetes mellitus who were new users of one of the SGLT2 inhibitors and a DKA rate of 0.41 cases per 100 person-years in patients with type 2 diabetes mellitus who were new users of one of the SGLT2 inhibitors, and from more than 500

cases of DKA in patients with type 1 diabetes mellitus associated with use of SGLT2 inhibitors that have been reported to the Food and Drug Administration Adverse Event Reporting System.

The remaining content of the ketoacidosis warning present in the current product labeling will need to be further modified accordingly.

- (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. We suggest the following wording be inserted in the patient Medication Guide immediately after the opening sentence of the Guide, which reads “**What is the most important information I should know about [name of drug]?**”:

**[Name of drug] should never be taken by patients with type 1 diabetes, for whom the drug is not approved, because of the greatly increased risk of life-threatening diabetic ketoacidosis (increased ketones in the blood or urine).**

- (5) Corresponding changes to “Limitation of Use” statements in the INDICATIONS AND USAGE section.

## **B. STATEMENT OF GROUNDS**

### **1. Legal standards**

The legal standards applicable to the actions requested in this petition are as follows:

The addition of a boxed warning to the product labeling of all SGLT2 inhibitors describing the increased risk of diabetic ketoacidosis when these drugs are used to treat type 1 diabetes and contraindicating their use for such patients would be predicated on meeting the standard for a contraindication which would be listed in the boxed warning as well as in the section on contraindications. Recent legislation adds a pathway for more expeditiously finalizing and implementing these urgent new warnings.

#### **a. Standard for a contraindication<sup>2</sup>**

According to FDA regulations and guidance, a drug should be contraindicated only in those clinical situations for which the risk of use (for example, certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

For observed adverse reactions, the following would ordinarily be reason to contraindicate a drug:

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<sup>2</sup> 21 C.F.R. § 201.57(c)(5) and Food and Drug Administration. 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. <https://www.fda.gov/media/71866/download>. Accessed June 19, 2020.

- (1) The risk of the adverse reaction in the clinical situation to which the contraindication applies, based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patient; and
- (2) The causal relationship between exposure to the drug and the adverse reaction is well established.

**b. Standard for a boxed warning<sup>3</sup>**

According to FDA regulations and guidance, the agency may require a boxed warning in the product labeling for prescription drugs for certain contraindications or serious warnings, particularly those that may lead to death or serious injury.

The agency advises that a boxed warning ordinarily is used for cases in which there is an adverse reaction so serious in proportion to the potential benefit from the drug that it should be considered in assessing the risks and benefits of using the drug or there is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug.

The FDA has stated that in order to include an adverse reaction as a warning in the product labeling, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established. In order to include such a warning as a boxed warning, evidence ordinarily must be based on clinical data.

In assessing evidence of a causal relationship for inclusion in the warnings section of a drug label, the FDA advises that factors to consider include (1) the frequency of reporting, (2) whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials, (3) evidence of a dose-response relationship, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the temporal association between the drug administration and the event, (6) the existence of dechallenge and rechallenge experience, and (7) whether the adverse event is known to be caused by related drugs.

**c. Newer standard for expedited finalizing of such urgent warnings<sup>4</sup>**

Section 505(o)(4) of the FDCA describes more recent requirements for safety labeling changes (SLCs) for approved drugs under the Food and Drug Administration Amendments Act of 2007 (FDAAA). These requirements are referred to as FDAAA SLCs.

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<sup>3</sup> 21C.F.R. § 201.57(c)(1) *and* Food and Drug Administration. 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. <https://www.fda.gov/media/71866/download>. Accessed June 19, 2020.

<sup>4</sup> Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act was added to the law with the Food and Drug Administration Amendments Act of 2007. The FDA described this provision and set forth policies and procedures for implementing it on July 10, 2019. <https://www.fda.gov/media/128660/download>. Accessed June 19, 2020.

Per section 505(o)(4) of the FDCA, the FDA is authorized to require and, if necessary, order application holders of certain approved drugs to make FDAAA SLCs based on new safety information that becomes available after approval of the drug. The statute imposes time frames for application holders to submit and for FDA staff to review such changes and gives the agency enforcement tools in instances of noncompliance.

Such new safety information concerning a serious risk or an unexpected serious risk associated with use of the drug of which the FDA has become aware (that may be based on a new analysis of existing information) since the drug was approved can be derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) of the FDCA), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FDCA; or other scientific data deemed appropriate by the FDA.

FDAAA established an urgent, shorter time frame for implementing such new safety labeling changes. Under the statute — once the FDA has agreed that a newly identified serious risk merits requiring or ordering a safety labeling change — the changes can be implemented as soon as 30 days after companies are notified of the FDA-proposed change. If companies submit objections or amendments, an additional 30 days are allowed before the FDA order can be implemented.

## **2. Regulatory background on SGLT2 inhibitors**

### **a. FDA-approved indications**

There currently are four FDA-approved SGLT2 inhibitors: canagliflozin (initial approval March 2013),<sup>5</sup> dapagliflozin (initial approval January 2014),<sup>6</sup> empagliflozin (initial approval August 2014),<sup>7</sup> and ertugliflozin (initial approval December 2017).<sup>8</sup> All are approved, in combination with diet and exercise, for the treatment of adults with type 2 diabetes. None are approved for the treatment of type 1 diabetes.

Dapagliflozin also is approved for treatment of adults with heart failure and a reduced cardiac ejection fraction (New York Heart Association class II-IV).<sup>9</sup>

### **b. History of SGLT2 inhibitor product labeling changes regarding limitation of use and DKA warnings**

The original FDA-approved product labeling for all four of the SGLT2 inhibitors, starting with canagliflozin, included the following statement:

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<sup>5</sup> Janssen Pharmaceutical Companies. Label: canagliflozin (INVOKANA). January 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/204042s0361bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204042s0361bl.pdf). Accessed June 19, 2020.

<sup>6</sup> AstraZeneca Pharmaceuticals. Label: dapagliflozin (FARXIGA). May 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/202293s0201bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s0201bl.pdf). Accessed June 19, 2020.

<sup>7</sup> Boehringer Ingelheim Pharmaceuticals. Label: empagliflozin (JARDIANCE). January 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/204629s0231bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204629s0231bl.pdf). Accessed June 19, 2020.

<sup>8</sup> Merck Sharp & Dohme Corp. Label: ertugliflozin (STEGLATRO). January 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/209803s0021bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209803s0021bl.pdf). Accessed June 19, 2020.

<sup>9</sup> AstraZeneca Pharmaceuticals. Label: dapagliflozin (FARXIGA). May 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/202293s0201bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s0201bl.pdf). Accessed June 19, 2020.

Limitation of Use: [SGLT2 inhibitor name] is not recommended [in/for] patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.<sup>10,11,12,13</sup>

This same statement remains in the current FDA-approved product labeling of all these drugs.

In May 2015, the FDA issued a drug safety communication advising that use of the then-FDA-approved SGLT2 inhibitors — canagliflozin, dapagliflozin, and empagliflozin — may lead to ketoacidosis.<sup>14</sup> The agency's communication reported that a search of the FDA Adverse Event Reporting System (FAERS) database had identified 20 cases of acidosis reported as DKA, ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors from March 2013 (approval of the first drug in the class) to June 6, 2014. Type 2 diabetes was noted as the indication in most of the cases, type 1 diabetes was noted as the indication in a few cases, and some cases did not specify the indication.

On December 4, 2015, the FDA issued an updated drug safety communication announcing that the agency had required, among other things, the addition of a warning about the risk of ketoacidosis to the product labeling for canagliflozin, dapagliflozin, and empagliflozin.<sup>15</sup> The agency's updated communication reported that a new search of FAERS from March 2013 to May 2015 had identified 73 cases of ketoacidosis associated with use of the SGLT2 inhibitors (canagliflozin [n=48], dapagliflozin [n=21], and empagliflozin [n=4]). In all cases, the patients were hospitalized or treated in the emergency department. Forty-four of the 73 cases occurred in patients with type 2 diabetes mellitus. Fifteen cases were reported in patients with type 1 diabetes, for which the SGLT2 inhibitors are not FDA-approved for use. In the 13 cases not reporting a diabetes type, 10 patients were treated concomitantly with oral antidiabetic agents, suggesting that these patients may have had type 2 diabetes mellitus. As a result, in December 2015, the product labeling for all three of the then-FDA-approved SGLT2 inhibitors were revised to include a new warning about the risk of drug-induced ketoacidosis in both type 1 and type 2 diabetes patients, excerpts of which read as follows:

## 5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization[,] have been identified in post marketing surveillance in patients with type

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<sup>10</sup> Janssen Pharmaceutical Companies. Label: canagliflozin (INVOKANA). March 2013.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/204042s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204042s000lbl.pdf). Accessed June 19, 2020.

<sup>11</sup> Bristol-Myers Squibb Company. Label: dapagliflozin (FARXIGA). January 2014.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/202293s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf). Accessed June 19, 2020.

<sup>12</sup> Boehringer Ingelheim Pharmaceuticals. Label: empagliflozin (JARDIANCE). August 2014.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/204629s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204629s000lbl.pdf). Accessed June 19, 2020.

<sup>13</sup> Merck Sharp & Dohme Corp. Label: ertugliflozin (STEGLATRO). December 2017.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/209803s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf). Accessed June 19, 2020.

<sup>14</sup> Food and Drug Administration. Drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. May 15, 2015.

<https://www.fda.gov/media/92185/download>. Accessed June 19, 2020.

<sup>15</sup> Food and Drug Administration. Drug safety communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. December 4, 2015.

<https://www.fda.gov/media/94822/download>. Accessed June 19, 2020.

1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including [SGLT2 inhibitor name]. [SGLT2 inhibitor name] is not indicated for the treatment of patients with type 1 diabetes mellitus [*see Indications and Usage (I)*]...

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and 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 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 due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified...

In patients treated with [SGLT2 inhibitor name] consider monitoring for ketoacidosis and temporarily discontinuing [SGLT2 inhibitor name] in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).<sup>16,17,18</sup>

In 2016, the warning about the risk of ketoacidosis in the FDA-approved product labeling for canagliflozin, dapagliflozin, and empagliflozin was further revised by inserting the following sentence in the first paragraph:

Fatal cases of ketoacidosis have been reported in patients taking [SGLT2 inhibitor name].<sup>19,20,21</sup>

When ertugliflozin was approved in December 2017, the initial FDA-approved product labeling included a warning about the risk of drug-induced ketoacidosis from SGLT2 inhibitor use that was similar to the warning in the product labeling for the three other SGLT2 inhibitors. One notable difference was the inclusion of data from clinical trials for ertugliflozin in the first paragraph of the warning:

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in clinical trials and postmarketing surveillance in

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<sup>16</sup> Janssen Pharmaceutical Companies. Label: canagliflozin (INVOKANA). December 2015.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/204042s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204042s013lbl.pdf). Accessed June 19, 2020.

<sup>17</sup> AstraZeneca Pharmaceuticals. Label: dapagliflozin (FARXIGA). December 2015.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/202293s008lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202293s008lbl.pdf). Accessed June 19, 2020.

<sup>18</sup> Boehringer Ingelheim Pharmaceuticals. Label: empagliflozin (JARDIANCE). December 2015.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/204629s007lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204629s007lbl.pdf). Accessed June 19, 2020.

<sup>19</sup> Janssen Pharmaceutical Companies. Label: canagliflozin (INVOKANA). August 2016.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/204042s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s022lbl.pdf). Accessed June 19, 2020.

<sup>20</sup> AstraZeneca Pharmaceuticals. Label: dapagliflozin (FARXIGA). August 2016.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/202293s010lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202293s010lbl.pdf). Accessed June 19, 2020.

<sup>21</sup> Boehringer Ingelheim Pharmaceuticals. Label: empagliflozin (JARDIANCE). December 2016.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/204629s008lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf). Accessed June 19, 2020.

patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors **and cases have been reported in [ertugliflozin]-treated patients in clinical trials. Across the clinical program, ketoacidosis was identified in 3 of 3,409 (0.1%) of [ertugliflozin]-treated patients and 0% of comparator-treated patients.** Fatal cases of ketoacidosis have been reported in patients taking SGLT2 inhibitors. STEGLATRO is not indicated for the treatment of patients with type 1 diabetes mellitus [*see Indications and Usage (1)*].<sup>22</sup> [Bolded emphasis added]

Finally, in January 2020, the warning about the risk of ketoacidosis in the FDA-approved product labeling for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin was revised to include the following:

For patients who undergo scheduled surgery, consider temporarily discontinuing [SGLT2 inhibitor name] for at least [3 or 4] days prior to surgery...

Consider monitoring for ketoacidosis and temporarily discontinuing [SGLT2 inhibitor 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 [SGLT2 inhibitor name].

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue [SGLT2 inhibitor name] and seek medical attention immediately if signs and symptoms occur.<sup>23,24,25,26</sup>

### **3. Evidence for markedly increased risk of DKA in patients with type 1 diabetes given SGLT2 or dual SGLT1/SGLT2 inhibitors**

#### **a. Randomized, placebo-controlled clinical trials to evaluate benefit-harm profile of SGLT2 or dual SGLT1/SGLT2 inhibitors in patients with type 1 diabetes for possible FDA approval**

A total of eight randomized, placebo-controlled, double-blind trials that each evaluated the safety and efficacy of one of the four SGLT2 inhibitors or one dual SGLT1/SGLT2 inhibitor as add-on therapy to insulin for patients with type 1 diabetes have been published in peer-reviewed scientific journals. Three of the four drugs tested — the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin — are currently FDA-approved for treatment of type 2 diabetes.

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<sup>22</sup> Merck Sharp & Dohme Corp. Label: ertugliflozin (STEGLATRO). December 2017.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/209803s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf). Accessed June 19, 2020.

<sup>23</sup> Janssen Pharmaceutical Companies. Label: canagliflozin (INVOKANA). January 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/204042s036lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204042s036lbl.pdf). Accessed June 19, 2020.

<sup>24</sup> AstraZeneca Pharmaceuticals. Label: dapagliflozin (FARXIGA). January 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/202293s021lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s021lbl.pdf). Accessed June 19, 2020.

<sup>25</sup> Boehringer Ingelheim Pharmaceuticals. Label: empagliflozin (JARDIANCE). January 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/204629s023lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204629s023lbl.pdf). Accessed June 19, 2020.

<sup>26</sup> Merck Sharp & Dohme Corp. Label: ertugliflozin (STEGLATRO). January 2020.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/209803s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209803s002lbl.pdf). Accessed June 19, 2020.

The fourth drug tested, sotagliflozin, which is a dual SGLT1/SGLT2 inhibitor, was never approved by the FDA for any indication.

The earliest such clinical trial was sponsored by the manufacturer of the first FDA-approved SGLT2 inhibitor, canagliflozin.<sup>27</sup> The trial was a phase 2 trial that randomized 351 subjects with type 1 diabetes who were taking insulin to receive canagliflozin, 100 milligrams (mg) or 300 mg, or a placebo once daily for up to 18 weeks. The manufacturer apparently never submitted data from the trial in order to obtain FDA approval of the drug for treatment of patients with type 1 diabetes, most likely in large part because the trial found a significantly increased rate of DKA in subjects who received canagliflozin. Of 234 subjects randomized to receive canagliflozin, 12 (5.1%) developed DKA, whereas none (0%) of the 117 subjects randomized to receive a placebo developed this condition.

The manufacturer of dapagliflozin sponsored two phase 3 trials that evaluated the safety and efficacy of the drug in patients with type 1 diabetes. The first trial randomized 833 subjects to receive dapagliflozin, 5 mg or 10 mg, or a placebo once daily for 52 weeks,<sup>28</sup> and the second randomized 813 subjects to receive dapagliflozin, 5 mg or 10 mg, or a placebo once daily for 24 weeks.<sup>29</sup> Among the 1,114 subjects randomized to receive dapagliflozin in the two trials combined, the total number of subjects who developed DKA was 34 (3.1%), whereas five of 532 subjects (0.1%) randomized to receive a placebo developed this condition. In 2019, the FDA rejected a supplemental new drug application (NDA) seeking approval of dapagliflozin to treat patients with type 1 diabetes largely because of concerns that the risk of harm from DKA outweighed the benefits of the drug.<sup>30</sup>

The manufacturer of empagliflozin sponsored two phase 3 trials that evaluated the safety and efficacy of the drug in patients with type 1 diabetes.<sup>31</sup> The first trial randomized 730 subjects to receive empagliflozin, 10 mg or 25 mg, or a placebo once daily for 52 weeks, and the second randomized 975 subjects to receive empagliflozin — 2.5 mg, 10 mg, or 25 mg — or a placebo once daily for 26 weeks. Among the 1,221 subjects randomized to receive empagliflozin in the two trials combined, the total number of subjects who developed DKA was 39 (3.2%), whereas six (1.2%) of 484 subjects randomized to a placebo developed this condition. As with dapagliflozin, the FDA in 2020 rejected a supplemental NDA seeking approval of empagliflozin

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<sup>27</sup> Henry RR, Thakkar P, Tong C, et al. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care*. 2015;38(12):2258-2265.

<sup>28</sup> Dandona P, Mathieu C, Phillip M, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. *Diabetes Care*. 2018;41(12):2552-2559.

<sup>29</sup> Mathieu C, Dandona P, Gillard P, et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. *Diabetes Care* 2018;41(9):1938-1946.

<sup>30</sup> AstraZeneca. Update on US regulatory decision for Farxiga in type-1 diabetes. July 15, 2019.

<https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2019/update-on-us-regulatory-decision-for-farxiga-in-type-1-diabetes-15072019.html>. Accessed June 19, 2020.

<sup>31</sup> Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: The EASE trials. *Diabetes Care*. 2018;41(12):2560-2569.

at the lowest tested dosage (2.5 mg daily) to treat patients with type 1 diabetes largely because of concerns that the risk of harm from DKA outweighed the benefits of the drug.<sup>32</sup>

Finally, the manufacturer of the dual SGLT1/SGLT2 inhibitor sotagliflozin, which has not been approved by the FDA for any use, in 2019 sought FDA approval of an NDA for the drug as an adjunct to insulin for treatment of adults with type 1 diabetes mellitus. Data from three phase 3 randomized, placebo-controlled clinical trials were submitted in support of the NDA.<sup>33,34,35</sup> Two trials that had identical designs together randomized 1,575 subjects to receive sotagliflozin, 200 mg or 400 mg, or a placebo once daily for 52 weeks, and the third randomized 1,402 subjects to receive sotagliflozin, 400 mg, or a placebo once daily for 52 weeks. Among the 1,748 subjects randomized to receive sotagliflozin in the three trials combined, the total number of subjects who developed DKA was 56 (3.2%), whereas five (0.4%) of the 1,229 subjects randomized to receive a placebo developed the condition. In 2019, the FDA rejected the NDA for sotagliflozin largely because of concerns that the risk of harm from DKA outweighed the benefits of the drug.<sup>36</sup>

The collective number of subjects with type 1 diabetes who developed DKA in these eight clinical trials was 141 (3.3%) of 4,317 subjects randomized to receive any of the four SGLT2 or dual SGLT1/SGLT2 inhibitors and 16 (0.7%) of 2,362 subjects randomized to receive a placebo.

Lu et al conducted a meta-analysis of ten randomized, placebo-controlled clinical trials that evaluated the safety and efficacy of SGLT2 or dual SGLT1/SGLT2 inhibitors as add-on therapy to insulin for patients with type 1 diabetes.<sup>37</sup> Their analysis included the eight clinical trials discussed above, as well two additional small phase 2 12-week, randomized, placebo-controlled clinical trials of sotagliflozin, which were published in abstract form only and were not peer-reviewed.<sup>38,39</sup> Lu et al found that the risk of DKA in the SGLT2 or dual SGLT1/SGLT2

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<sup>32</sup> Boehringer Ingelheim. US FDA issues complete response letter for empagliflozin 2.5 mg as adjunct to insulin for adults with type 1 diabetes. March 20, 2020. <https://www.boehringer-ingelheim.us/press-release/us-fda-issues-complete-response-letter-empagliflozin-25-mg-adjunct-insulin-adults-type>. Accessed June 19, 2020.

<sup>33</sup> Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: The North American inTandem1 study. *Diabetes Care*. 2018;41(9):1970-1980.

<sup>34</sup> Danne T, Cariou B, Banks P, et al. HbA1c and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 study. *Diabetes Care*. 2018;41(9):1981-1990.

<sup>35</sup> 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):2337-2348.

<sup>36</sup> Tucker ME. FDA turns down sotagliflozin for type 1 diabetes. March 22, 2019. <https://www.medscape.com/viewarticle/910851>. Accessed June 19, 2020.

<sup>37</sup> Lu J, Tang L, Meng H, et al. 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*. 2019;35:e3169.

<sup>38</sup> Bode B, Banks P, Sawhney S, Strumph P. 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). *Pediatr Diabetes*. 2017;18((Bode B.) Atlanta Diabetes Associates, Atlanta, GA, United States):25-26. This trial enrolled 85 subjects with type 1 diabetes who were randomly assigned to sotagliflozin, 400 mg, or a placebo once daily for 12 weeks.

<sup>39</sup> Baker C, Wason S, Banks P, et al. 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*. 2017;60(1):S409. This trial enrolled 141 subjects with type 1 diabetes who were randomly assigned to sotagliflozin, 75 mg, 200 mg, or 400 mg, or a placebo once daily for 12 weeks.

inhibitor-treated subjects was significantly increased compared with placebo-treated subjects (relative risk 3.11; 95% CI, 2.11-4.58).

For all three SGLT2 inhibitors and the one dual SGLT1/SGLT2 inhibitor, the improvements in HbA1c seen in clinical trials of the drugs in subjects with type 1 diabetes were small and, according to a review, these clinical trials showed a consistent and progressive loss of the previously achieved HbA1c improvement between 24 and 52 weeks.<sup>40</sup>

The manufacturer of a fifth SGLT2 inhibitor, ertugliflozin, approved for treatment of type 2 diabetes in December 2017, has neither published nor, to our knowledge (based on a search of the ClinicalTrials.gov database), performed any study involving patients with type 1 diabetes as did the manufacturers of all three other SGLT2 inhibitors and the one dual SGLT1/SGLT2 inhibitor.

**b. FDA analysis of cases of DKA in patients with type 1 diabetics using SGLT2 inhibitors that were reported to FAERS through September 11, 2018; Public Citizen's recent update of cases through the end of 2019.**

The FDA's FAERS database is a repository for drug-related adverse event reports sent to the agency by pharmaceutical companies, pharmacists, physicians, and others.

The table below provides data on the number of DKA cases associated with the use of SGLT2 inhibitors in patients with type 1 diabetes reported to FAERS by year that was presented by the FDA during the January 17, 2019, meeting of the agency's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), which was convened to make recommendations concerning the possible approval of sotagliflozin.<sup>41</sup> The table was updated to include counts of additional cases through the end of 2019 through a review of the FAERS Public Dashboard by Public Citizen. We identified all cases of DKA associated with the use of an SGLT2 inhibitor in patients with type 1 diabetes that had been reported to FAERS and had an initial report date later than September 11, 2018, which was the end date for the case count data provided by the FDA to the EMDAC.

The FDA reported to the EMDAC that through September 11, 2018, 444 cases of DKA associated with use of an SGLT2 inhibitor in patients with type 1 diabetes had been reported to FAERS. Our review of FAERS data through the end of 2019 revealed 106 additional such DKA cases reported to FAERS. There were 23 additional cases with an initial report date in 2018 after September 11 and 83 cases with an initial report date in 2019, bringing the total number of cases to 550.

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<sup>40</sup> Taylor SI, Blau JE, Rother KI, Beitelshes AL. SGLT2 inhibitors as adjunctive therapy for type 1 diabetes: Balancing benefits and risks. *Lancet Diabetes Endocrinol.* 2019;7(12):949-958.

<sup>41</sup> Food and Drug Administration. FDA briefing document: Endocrinologic and Metabolic Drugs Advisory Committee meeting. January 17, 2019. <https://www.fda.gov/media/121286/download>. Accessed June 16, 2020. PDF page 107.

**Table: Cases of DKA Associated With the Use of SGLT2 Inhibitors in Patients With Type 1 Diabetes Reported to FAERS by Year**

| FDA Report Year | Number of Cases |
|-----------------|-----------------|
| <=2013          | 2               |
| 2014            | 11              |
| 2015            | 163             |
| 2016            | 130             |
| 2017            | 85              |
| 2018            | 76              |
| 2019            | 83              |
| All years       | 550             |

Starting in January 2016 — following the FDA-mandated addition of the new warning about the risk of ketoacidosis to the product labeling for all FDA-approved SGLT2 inhibitors in December 2015 — through the end of 2019, a total of 374 cases of DKA associated with use of SGLT2 inhibitors in patients with type 1 diabetes were reported to the FDA, whereas 176 such cases had been reported through the end of 2015 before the new ketoacidosis warnings were added to the product labeling.

The agency reported that among the 444 DKA cases that were presented by the FDA to EMDAC, the DKA adverse events resulted in hospitalization in 336 cases and were life-threatening in 50 cases.<sup>42</sup> Among the 106 additional DKA cases reported to the FDA after September 11, 2018, through the end of 2019, the DKA adverse events resulted in hospitalization in 75 cases and were life-threatening in 18 cases. Thus, among the 550 cases of DKA associated with the use of SGLT2 inhibitors that were reported to FAERS through 2019, the DKA adverse events resulted in hospitalization in 411 cases and were life-threatening in 68 cases.

### **c. Data from FDA’s Sentinel System**

Researchers from the FDA’s Office of Surveillance and Epidemiology and the Department of Population Medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute recently assessed the rates of DKA associated with use of SGLT2 inhibitors in patients with type 1 or type 2 diabetes using data from the Sentinel System, which includes administrative claims data from more than 100 million U.S. patients who are enrolled in commercial or public health insurance plans.<sup>43</sup> The researchers identified all new users of SGLT2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) in the Sentinel System database from March 2013 (the month when canagliflozin was approved by the FDA) to June 2018. Among 475,527 initiators of one of the three drugs, 2,379 (0.5%) met narrowly defined criteria and 4,375 (0.9%) met broadly defined criteria for type 1 diabetes, an off-label indication for which the drugs have never been approved.

<sup>42</sup> *Ibid.* PDF page 137.

<sup>43</sup> Hampp C, Swain RS, Horgan C, et al. Use of sodium-glucose cotransporter 2 inhibitors in patients with type 1 diabetes and rates of diabetic ketoacidosis. *Diabetes Care.* 2020;43(1):90-97.

Among the 2,379 patients meeting narrowly defined criteria for type 1 diabetes who were new users of one of the three SGLT2 inhibitors, the DKA rate was 7.3 events per 100 person-years. Among the 4,375 patients meeting broadly defined criteria for type 1 diabetes who were initiators of one of these drugs, the DKA rate was 4.5 events per 100 person-years. In contrast, among 369,154 patients with type 2 diabetes who were new users of one of the same three SGLT2 inhibitors, the DKA rate was 0.41 cases per 100 person-years.<sup>44</sup> We note that such a difference in DKA rates between patients with type 1 and type 2 diabetes would be expected given the difference in the underlying pathophysiology of the two types of diabetes and the fact the DKA is classically a complication seen mainly in type 1 diabetes.

Summarizing the postmarketing evidence of harm to patients with type 1 diabetes using FDA-approved SGLT2 inhibitors from both the FAERS data and the Sentinel System study, FDA medical officer Mitra Rauschecker, M.D., stated the following in a presentation at the January 17, 2019, meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee:

- FAERS and Sentinel analyses: demonstrate the risks of DKA with the SGLT2 inhibitor class in a postmarket (real-world) setting.
- Among patients who used SGLT2 inhibitors off-label, the risk for DKA was notable, especially among patients under the age of 45.
- DKA events in patients with type 1 diabetes patients using an SGLT2 inhibitor can be severe and can be associated with serious complications including acute kidney injury, respiratory failure, coma, and may even lead to death.<sup>45</sup>

#### **4. Summary of evidence of avoidable DKA harm; necessity and legal basis for an immediate boxed warning contraindicating SGLT2 inhibitors for treatment of patients with type 1 diabetes patients**

There is clear evidence from eight large randomized, placebo-controlled, double-blind clinical trials that the use of an SGLT2 or dual SGLT1/SGLT2 inhibitor as add-on therapy to insulin for patients with type 1 diabetes markedly increases the risk of DKA. The collective number of subjects who developed DKA in these eight trials was 141 (3.3%) of 4,317 subjects treated with an SGLT2 or dual SGLT1/SGLT2 inhibitor, whereas 16 (0.7%) of 2,362 placebo-treated subjects developed this condition. In addition, a published meta-analysis of these eight clinical trials plus two additional small unpublished trials found that the risk of DKA in the SGLT2 or dual SGLT1/SGLT2 inhibitor-treated patients was significantly increased compared with placebo-treated subjects (relative risk 3.11; 95% CI, 2.11-4.58).

The manufacturers of two SGLT2 inhibitors and one dual SGLT1/SGLT2 inhibitor applied for FDA approval for use of the drugs as add-on therapy to insulin for type 1 diabetes, and in each case, the FDA rejected the application. Thus, the FDA found these drugs too dangerous to be used to treat patients with type 1 diabetes. The manufacturer of a third SGLT2 inhibitor, canagliflozin, never sought FDA approval for type 1 diabetes.

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<sup>44</sup> *Ibid.* See Supplementary Table 3.

<sup>45</sup> Food and Drug Administration. Presentation slides for the January 17, 2019 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. <https://www.fda.gov/media/121289/download>. Accessed June 19, 2020. Slide 115.

During the four years since December 2015, when the FDA required the addition of the new warning about the risk of ketoacidosis to the product labeling for all approved SGLT2 inhibitors, the FDA received reports of 374 additional cases of DKA in patients with type 1 diabetes who were prescribed these drugs off-label, strongly pointing toward the inadequacy of the current label warnings.

The current product labeling for all four approved SGLT2 inhibitors fails to convey the strong evidence that these drugs cause a large increase in life-threatening DKA, particularly the data from the eight large randomized, placebo-controlled clinical trials testing these drugs in subjects with type 1 diabetes. In addition, there is no mention of the real-world finding from the FDA's Sentinel System study, which found a DKA rate of 7.3 events per 100 person-years in patients meeting narrowly defined criteria for type 1 diabetes mellitus who were new users of an SGLT2 inhibitor and a DKA rate of 0.41 cases per 100 person-years in patients with type 2 diabetes mellitus who were new users of an SGLT2 inhibitor. The most glaring omission in the product labeling, however, is the inexcusable failure to contraindicate all SGLT2 inhibitors for use in patients with type 1 diabetes because of the well-documented evidence of harm.

The only feasible, health-protective action that the FDA can take to decrease preventable life-threatening DKA caused by continued off-label prescribing to patients with type 1 diabetes is to add a boxed warning to the product labeling for all SGLT2 inhibitors that explicitly contraindicates the use of these drugs in such patients.

The laws and regulations enabling the FDA to take this important action make it quite clear that the agency has the authority to promptly order a boxed warning contraindicating all SGLT2 inhibitors for use in patients with type 1 diabetes based on the current evidence of harm due to continued off-label prescribing. More than four years since the warnings about the risk of DKA were added to the product labeling, this labeling has been grossly inadequate in deterring such dangerous prescribing.

For the above reasons, we hereby petition the FDA, under Sections 502 and 505(o)(4) of the FDCA (21 U.S.C. §§ 352 and 355(o)(4)) and under FDA regulations at 21 C.F.R. §§ 10.30, 201.56, 201.57(c)(1), and 201.57(c)(5) to request that the Commissioner of Food and Drugs immediately require that the following changes be made to the product labeling for all FDA-approved SGLT2 inhibitors, including all combination products containing these drugs:

- (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. We suggest the following wording for the requested boxed warning:

**WARNING: CONTRAINDICATION FOR TYPE 1 DIABETES  
MELLITUS**

**Increased Risk of Diabetic Ketoacidosis (DKA) in Patients with Type 1  
Diabetes Mellitus Who Use [Name of Drug]: Use of [name of drug] in  
patients with type 1 diabetes mellitus, for whom the drug is not approved, is**

**contraindicated. In eight large randomized, placebo-controlled, double-blind clinical trials that each assessed the safety and efficacy of one of three SGLT2 inhibitors or one dual SGLT1/SGLT2 inhibitor as add-on therapy to insulin for patients with type 1 diabetes, the collective number of subjects who developed DKA was 141 (3.3%) of 4,317 subjects treated with an SGLT2 or dual SGLT1/SGLT2 inhibitor and 16 (0.7%) of 2,362 placebo-treated subjects. A published meta-analysis of these eight clinical trials and two additional small unpublished trials found that the risk of DKA in the SGLT2 or dual SGLT1/SGLT2 inhibitor-treated subjects was significantly increased compared with placebo-treated subjects (relative risk 3.11; 95% CI, 2.11-4.58) [see Warnings and Precautions].**

(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. We suggest the following wording for the new bullet:

- Use of [name of drug] in patients with type 1 diabetes mellitus, for whom the drug is not approved, is contraindicated. *[see Warnings and Precautions]*

(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 and briefly reviewing the strong evidence for this contraindication. We suggest the following wording for the requested warning be added at the beginning of the ketoacidosis warning subsection:

Use of [name of drug] in patients with type 1 diabetes mellitus, for whom the drug is not approved, is contraindicated because of the marked increase in the risk of DKA. In eight large randomized, placebo-controlled, double-blind clinical trials that each assessed the safety and efficacy of one of three SGLT2 inhibitors or one dual SGLT1/SGLT2 inhibitor as add-on therapy to insulin for patients with type 1 diabetes, the collective number of subjects who developed DKA was 141 (3.3%) of 4,317 subjects treated with an SGLT2 or dual SGLT1/SGLT2 inhibitor and 16 (0.7%) of 2,362 placebo-treated subjects. A published meta-analysis of these eight clinical trials and two additional small unpublished trials found that the risk of DKA in the SGLT2 or dual SGLT1/SGLT2 inhibitor-treated subjects was significantly increased compared with placebo-treated subjects (relative risk 3.11; 95% CI, 2.11-4.58).

Additional evidence for this life-threatening risk comes from an FDA-conducted real-world study of Sentinel System data, which found a DKA rate of 7.3 events per 100 person-years in patients meeting narrowly defined criteria for type 1 diabetes mellitus who were new users of one of the SGLT2 inhibitors and a DKA rate of 0.41 cases per 100 person-years in patients with type 2 diabetes mellitus who were new users of one of the SGLT2 inhibitors, and from more than 500 cases of DKA in patients with type 1 diabetes mellitus associated with use of

SGLT2 inhibitors that have been reported to the Food and Drug Administration Adverse Event Reporting System.

The remaining content of the ketoacidosis warning present in the current product labeling will need to be further modified accordingly.

- (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. We suggest the following wording be inserted in the patient Medication Guide immediately after the opening sentence of the Guide, which reads “**What is the most important information I should know about [name of drug]?**”:

**[Name of drug] should never be taken by patients with type 1 diabetes, for whom the drug is not approved, because of the greatly increased risk of life-threatening diabetic ketoacidosis (increased ketones in the blood or urine).**

- (5) Corresponding changes to “Limitation of Use” statements in the INDICATIONS AND USAGE section.

### C. ENVIRONMENTAL IMPACT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

### D. ECONOMIC IMPACT

Will be submitted upon request.

### E. CERTIFICATIONS

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.



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