



NATIONAL PBM BULLETIN

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DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

SGLT2 INHIBITORS AND POTENTIAL RISK OF ACIDOSIS

I. ISSUE

FDA is investigating postmarketing reports of sodium-glucose cotransporter-2 (SGLT2) inhibitor use and potential development of a high anion gap metabolic acidosis accompanied by elevation in urine or serum ketones and will determine if changes are needed in the labeling for this class of drugs.

II. BACKGROUND

SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are oral hypoglycemic agents approved by the FDA for use as single-ingredient products or as combination products with other antidiabetic agents to improve glycemic control in Type 2 diabetics adjunctively with diet and exercise. These agents work at the level of the kidney to reduce reabsorption of filtered glucose from the tubular lumen, thus increasing the urinary glucose excretion. SGLT2 inhibitors are not FDA-approved to treat patients with type 1 diabetes mellitus.

III. DISCUSSION

The FDA Adverse Event Reporting System (FAERS) database identified 20 cases of diabetic ketoacidosis (DKA), ketoacidosis, or ketosis reported with SGLT2 inhibitors since approval of the first drug in this class in March 2013 through June 6, 2014.

- Median time to onset of symptoms following initiation of drug therapy was 2 weeks (range 1 to 175 days).
- Atypically, glucose levels were only mildly elevated at less than 200 mg/dL in some reports (patients with type 1 diabetes who have DKA usually have glucose levels above 250 mg/dL; DKA does not routinely occur in patients with type 2 diabetes).
- Half of the cases reported potential triggers for DKA, including acute illness or recent significant changes such as infection, urosepsis, trauma, reduced caloric or fluid intake, and reduced insulin dose.
- Most cases reported a high anion gap metabolic acidosis accompanied by elevated blood or urine ketones possibly precipitated by hypovolemia, acute renal impairment, hypoxemia, reduced oral intake, or a history of alcohol use.
- All cases resulted in emergency room visits or hospitalization to treat the acidosis.

IV. PROVIDER RECOMMENDATIONS

FDA recommends that health care providers:

- Be aware of the possible development of a high anion gap metabolic acidosis accompanied by elevation in urine or serum ketones associated with the use of SGLT2 inhibitors, even if glucose levels are not very high as is typical for DKA.
- Evaluate any presence of acidosis, including ketoacidosis, for appropriate action:
 - discontinue SGLT2 inhibitors if acidosis is confirmed;
 - correct the acidosis and monitor glucose levels;
 - treat and correct factors that may have precipitated or contributed to the metabolic acidosis.
- Educate patients and caregivers of the signs and symptoms of metabolic acidosis, such as tachypnea or hyperventilation, anorexia, abdominal pain, nausea, vomiting, lethargy, or mental status changes, and instruct them to seek medical attention immediately if these symptoms occur.

Providers should continue to report any adverse reactions with the use of SGLT2 inhibitors by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. <http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm> . (Accessed 5/15/2015).

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., primary care providers, endocrinology, Emergency Department providers, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).