P01/2016/AT
14.03.2016

Direct Healthcare Professional Communication

Updated advice on the risk of diabetic ketoacidosis during treatment with SGLT2 inhibitors

(Invokana (canagliflozin), Vokanamet (canagliflozin/metformin), Forxiga (dapagliflozin), Xigduo (dapagliflozin/metformin), Jardiance (empagliflozin), Synjardy (empagliflozin/metformin))

Dear Pharmacist,

In agreement with the European Medicines Agency (EMA) and the Medicines Authority, Janssen-Cilag International N.V., AstraZeneca AB and Boehringer Ingelheim International GmbH would like to inform you of the latest recommendations regarding the risk of diabetic ketoacidosis (DKA) during treatment with SGLT2 inhibitors (canagliflozin, dapagliflozin or empagliflozin). This follows on the outcome of an evaluation by the EMA of the risk of diabetic ketoacidosis during treatment with SGLT2 inhibitors.

Rare but serious, sometimes life-threatening and fatal cases of diabetic ketoacidosis have been reported in patients on SGLT2 inhibitor treatment for type 2 diabetes. In a number of these reports, the presentation of the condition was atypical with only moderately increased blood glucose levels observed. Such atypical presentation of diabetic ketoacidosis in patients with diabetes could delay diagnosis and treatment.

Summary of updated advice

- The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Prescribers should inform patients of signs and symptoms of metabolic acidosis and advise them to immediately seek medical advice if they develop such signs and symptoms.

- In patients where DKA is suspected or diagnosed, treatment with SGLT2 inhibitors should be discontinued immediately.
- Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.
- Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. In both cases, treatment with SGLT2 inhibitors may be restarted once the patient's condition has stabilised.

The information for the healthcare professionals in the summary of product characteristics (SmPC) and the information for patients in the package leaflet will be updated accordingly.

Further information on the safety concern and the recommendations

The majority of the reports of diabetic ketoacidosis in patients treated with SGLT2 inhibitors required hospitalization. To date, many of them have occurred during the first 2 months of treatment. In some cases, just
before or at the same time as the ketoacidosis occurred, patients experienced dehydration, low food intake, weight loss, infection, surgery, vomiting, a decrease in their insulin dose or poor control of diabetes. In a number of cases atypical moderately increased glucose values or glucose values below 14 mmol/l (250 mg/dl) were reported, whereas hypoglycemia was reported in one case. There were also cases of ketoacidosis shortly after discontinuation of SGLT2 inhibitors.

The underlying mechanism for SGLT2 inhibitor-associated diabetic ketoacidosis is not established. Diabetic ketoacidosis usually develops when insulin levels are too low. Diabetic ketoacidosis occurs most commonly in patients with type 1 diabetes and is usually accompanied by high blood glucose levels (>14 mmol/l). However, the cases referred to above concern patients with type 2 diabetes and in a number of cases blood glucose levels were only slightly increased, in contrast to typical cases of diabetic ketoacidosis.

<u>Further recommendations:</u>

Before initiating treatment with SGLT2 inhibitors, factors in the patient history that may predispose to ketoacidosis should be considered. These factors include:

- a low beta-cell function reserve (e.g. Type 2 diabetes patients with low C-peptide, latent autoimmune disease in adults (LADA) or patients with a history of pancreatitis),
- conditions that lead to restricted food intake or severe dehydration,

- sudden reduction in insulin,
- increased insulin requirements due to acute medical illness,
- surgery,
- alcohol abuse

SGLT2 inhibitors should be used with caution in these patients. In addition, patients should be informed of the above risk factors. A substantial proportion of the cases concerned off-label use in patients with type 1 diabetes. Prescribers are reminded that type 1 diabetes is not an approved indication for SGLT2 inhibitors. Based on limited clinical data ketoacidosis appears to occur with common frequency in patients with type 1 diabetes.

Call for reporting

Any suspected adverse reactions and medication errors can be reported to the Medicines Authority or to the license holders of SGLT-2 containing products. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Medicines Authority Post-licensing Directorate, 203, Level 3, Rue D'Argens, Gżira GŻR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Company contact points

Contact point details for further information and ADR reporting are given in the product information of the medicine (SmPC and Package Leaflet).

Yours sincerely,

The Post Licensing Directorate
Medicines Authority

Disclaimer
This Direct Healthcare Professional Communication has been submitted to you on behalf of *AstraZeneca AB, Boehringer Ingelheim International GmbH and Janssen-Cilag International N.V.*

QUESTIONNAIRE: THE PERCEPTIONS OF MALTESE DOCTORS AND PHARMACISTS ON MEDICATION ERRORS

P02/2016/AT
14.03.2016

Dear Pharmacist,

The Medicines Authority would like to invite you to participate in a survey by answering the attached very short questionnaire. The aim is to gather information regarding medication errors, specifically to identify human and system factors which are considered as bearing a causal link to medication errors.

The results of this study could help identify targeted areas for improvement by regulators, policy makers and healthcare professionals when taking action against medication errors.
Therefore we kindly invite your anonymous participation. The survey may be returned by folding it together with this letter (address side up), stapling the ends and then posting (no stamp required) by March 31st 2016.
If you have already filled in this questionnaire we extend our thanks and kindly ask that you ignore this survey.

In addition, doctors are encouraged to report any ADRs and medication errors using the Medicines Authority's online form at **http://www.medicinesauthority.gov.mt/adrportal.**
Healthcare professionals are reminded that medication error reports are made anonymous after follow up and kept in strict confidence by the Medicines Authority.

We thank you for your vigilance and look forward to hearing your opinion,

Amy Tanti B.Pharm (Hons.) MSc.PH

Safety Assessor/ The Medicines Authority

203, Level 3, Rue D'Argens, Il-Gżira, GZR 1368, Malta

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www.medicinesauthority.gov.mt

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Pharmacovigilance Section

Post-licensing Directorate

Medicines Authority

203, Level 3

Rue D'Argens

Gzira GZR 1368

Pharmacists' Opinion on Prescribing Errors

1. Demographics

1. Gender: M/F | 2. Age | 3. Years of experience

4. Area(s) of practise (ex. community pharmacy, hospital pharmacy)

5. On average, how many hours a week do you spend in practice?

2. Pharmacists' opinions on dispensing errors

	Yes	No
6. Do you believe that the RISK of errors in dispensing is increasing in pharmacy practise?	☐	☐
8. Do you believe that ACTUAL errors in dispensing are becoming more common	☐	☐

9. We are interested in identifying variables that pharmacists perceive as being associated with dispensing errors. Do you believe that each of the following factors is associated with the occurrence of errors in dispensing? Answer each by marking the scale provided.

	No association	Low association	Fair association	High association	Very High association
(a) Doctors handwriting	☐	☐	☐	☐	☐
(b) Similar or confusing drug names	☐	☐	☐	☐	☐
(c) The existence of generic brands	☐	☐	☐	☐	☐
(d) Distractions due to administration / clerical requirements	☐	☐	☐	☐	☐
(e) Distractions from other staff	☐	☐	☐	☐	☐
(f) Distractions from the patients	☐	☐	☐	☐	☐
(g) Pharmacist overwork	☐	☐	☐	☐	☐
(h) pharmacist fatigue from any cause	☐	☐	☐	☐	☐
(i) Job dissatisfaction	☐	☐	☐	☐	☐
(j) High patient volume	☐	☐	☐	☐	☐
(k) Sole pharmacist (compared with 2 or more pharmacists present at one time)	☐	☐	☐	☐	☐
(j) Noise	☐	☐	☐	☐	☐
(m) Interruptions	☐	☐	☐	☐	☐
(n) Design of work surroundings	☐	☐	☐	☐	☐
(o) Lack of availability of IT resources	☐	☐	☐	☐	☐
(p) Insufficient technical resources	☐	☐	☐	☐	☐

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(q) Lack of privacy	☐	☐	☐	☐	☐
(r) Non-professional activities occurring in the vicinity	☐	☐	☐	☐	☐
(s) Insufficient time to talk to patients	☐	☐	☐	☐	☐
Other (please specify)					

10. Which of the following factors would you nominate as being important in minimising the risk of dispensing errors? Please rate the importance of each by ticking on the scale provided

	Not important	Of Low importance	Uncertain of importance	Fairly important	Very important
(a) Reducing workload on pharmacists	☐	☐	☐	☐	☐
(c) Keeping one's knowledge of drugs up to date	☐	☐	☐	☐	☐
(c) Avoiding interruptions	☐	☐	☐	☐	☐
(d) Having medicine names that are distinctive	☐	☐	☐	☐	☐
(e) Having distinctive packaging within the same corporate livery	☐	☐	☐	☐	☐
(f) Getting information from the pharmaceutical industry	☐	☐	☐	☐	☐
(g) Privacy when seeing patients	☐	☐	☐	☐	☐
Other (please specify)					

11. Approximately how many continuous hours per day do you think can be safely spent in dispensing?

	Yes	No
12. Do you think there should be a regulatory requirement on the amount of continuous dispensing hours that can be done per day?	☐	☐
13. Are you aware of any dispensing errors in your place of practice during the past year?	☐	☐

If yes; 2. Approximately how many errors in your place of practice are you aware of?

14. Was there a common causative factor that you can identify? If yes, please list

15. Do you have any further comments or suggestions on the issue of dispensing errors?

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