June 2015

Dear Health Care Professional,

הנדון: <u>סיכון לקטואצידוזיס סוכרתית (Diabetic ketoacidosis, DKA) בשימוש בתכשירים מעכבי SGLT2</u>

חברת יאנסן וחברת אסטרזנקה, בעלות הרישום של תכשירים מעכבי SGLT2 הרשומים בישראל Invokana (canagliflozin) ו-Forxiga (dapagliflozin) מעוניינות ליידע את הצוות הרפואי במידע הבא:

- לאחרונה דווחו בעולם ובישראל מקרי קטואצידוזיס סוכרתית (DKA), בחלקם מסכני חיים, במטופלים במעכבי SGLT2
- כמחצית מהמקרים אירעו במהלך החודשיים הראשונים של הטיפול
- כשליש מהמקרים אירעו במטופלים עם סכרת מסוג I בהם מעכבי SGTL2 ניתנים שלא בהתאם להתוויה
- בניגוד להופעה הקלאסית של קטואצידוזיס המלווה ברמות גלוקוז גבוהות, בחלק מהמקרים העלייה ברמות הגלוקוז הייתה מתונה
- יש לידע את המטופלים במעכבי SGTL2 בנוגע לסימנים אפשריים של אצידוזיס ביניהם בחילה, הקאות, אנורקסיה, כאב בטן, צמא מוגבר, קשיי נשימה, בלבול, עייפות חריגה או ישנוניות ולהנחות אותם לפנות באופן מיידי לטיפול רפואי במקרה של הופעת סימנים ותסמינים אלו
- מומלץ לבצע בדיקת קטונים במטופלים במעכבי SGTL2 עם הופעת סימנים של אצידוזיס
- יש להפסיק את השימוש במעכבי SGTL2 עם הופעת אצידוזיס

Janssen (J-C healthcare) and AstraZeneca , the MAH of INVOKANA (canagliflozin) and FORXIGA (dapagliflozin) respectively, would like to inform you of new safety information for prescription medicines containing canagliflozin and dapagliflozin, which are inhibitors of sodium glucose co-transport 2 (SGLT2) approved as oral antihyperglycemic agents for the treatment of patients with type 2 diabetes mellitus.

Summary:

Rare, but serious and sometimes life-threatening cases of diabetic ketoacidosis (DKA) have been reported in patients on SGLT2 inhibitor treatment (canagliflozin and dapagliflozin) for type 2 diabetes. A Drug Safety Communication (DSC) on this topic was first published by the FDA in US on the 15th of May 2015 and subsequently on 12th June 2015 the European Medicines Agency (EMA) started a procedure to evaluate the risk of ketoacidosis for the SGLT2 inhibitor class of drugs.

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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.

Patients on SGLT2 inhibitors should be tested for ketones when they present with symptoms of acidosis such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness in order to prevent delayed diagnosis and patient management.

Cases of diabetic ketoacidosis were also reported in patients with type 1 diabetes who were given SGLT2 inhibitors. Prescribers are reminded that type 1 diabetes is **not** an approved indication for this drug class.

Further information on the safety concern:

Serious and sometimes life-threatening cases of diabetic ketoacidosis in patients under treatment with SGLT2-inhibitors (including canagliflozin and dapagliflozin) have been reported, the majority of them requiring hospitalization. Of the cases reported, up to half of them occurred during the first 2 months of treatment. One third of the cases concerned off-label use in patients with type 1 diabetes. 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 or 250 mg/dl). However, in a number of cases described above blood glucose levels were only slightly increased, in contrast to typical cases of diabetic ketoacidosis.

The companies will be working in collaboration with the FDA and EMA to further evaluate the risk of DKA. Any new advice will be communicated promptly.

Recommendation :

SGLT2 inhibitors should be used according to the relevant Product Information leaflet. Prescribers should inform patients of signs and symptoms of metabolic acidosis and advise them to immediately seek medical advice if they experience any such signs and symptoms.

It is recommended that patients taking SGLT2 inhibitors should be tested for ketones when they present with signs or symptoms of metabolic acidosis in order to prevent delayed diagnosis and patient management.

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Discontinue SGLT2 inhibitors if acidosis is confirmed and take appropriate measures to correct the acidosis and to monitor glucose levels.

Adverse event reporting:

Report adverse events involving SGLT2 inhibitors to the following:

Ministry of health:

The Risk Management and Drug Information Department is following safety reports from Israel and the world and is evaluating recommendations for the continues use of these products. Please report adverse events to the ministry of health via on line form found at the following link **http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic%40moh.health.gov.il** or to **ADR@moh.health.gov.il .**

Adverse events for **Invokana** can be reported directly to Janssen, to Mr. Tzaphrir Cohen:

e-mail: tcohen@its.jnj.com Tel: 0544-307281

Adverse events for **FORXIGA** can be reported directly to Astra Zeneca, to the following e-mail address: safety.Israel@astrazeneca.com or faxed to 097406527.

Link to the FDA announcement:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm446994.htm

Link to the EMA information:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/SGLT2_inhibitors/human_referral_prac_000052.jsp&mid=WC0b01ac05805c516f

Sincerely,

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