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Direct healthcare-professional communication (DHPC)

9 June, 2016

Updated advice on the risk of diabetic ketoacidosis during treatment with (sodium glucose co-transporter 2 inhibitors) including Jardiance® (empagliflozin) and Synjardy® (empagliflozin/ Metformin Hydrochloride).

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Dear Healthcare professional,

In agreement with Saudi Food and Drug Authority, Boehringer Ingelheim would like to inform you about the latest recommendations regarding the risk of diabetic ketoacidosis (DKA) during treatment with all SGLT2 inhibitors including (empagliflozin).

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.

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- 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 hospitalized 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 stabilized.

For more information please refer to the summary of product characteristics (SmPC) and the patient information leaflet (PIL)

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, and 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.

Further recommendations:

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

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- 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, patient 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 adverse reactions should be reported in accordance with the Saudi Vigilance spontaneous reporting system to:

The National Pharmacovigilance and Drug Safety Centre NPC
Email: npc.drug@sfda.gov.sa
Fax: +966112057662
Toll free phone: 8002490000

In addition, suspected adverse reactions related Boehringer Ingelheim products may be reported to Boehringer Ingelheim Pharmacovigilance department:
Email: PV_local_Saudi_Arabia@boehringer-ingelheim.com
Phone: +966-11-207 8275

Sincerely,

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