Letter to Healthcare Practitioners

9 July 2015

Dear Dr

AstraZeneca wish to inform you of the following important safety information regarding Forxiga™ (dapagliflozin 10mg).

Summary

- Serious, sometimes life-threatening cases of diabetic ketoacidosis have been reported in patients on SGLT2 inhibitor treatment (canagliflozin, dapagliflozin or empagliflozin) 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.
- Patients on SGLT2 inhibitors should be tested for ketones when they present with symptoms of acidosis 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 and the recommendations

Serious and sometimes life-threatening cases of diabetic ketoacidosis in patients under treatment with SGLT2-inhibitors (canagliflozin, dapagliflozin and empagliflozin) have been reported, the majority of them requiring hospitalisation. 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 were reported, whereas hypoglycaemia 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, in a number of cases described above blood glucose levels were only slightly increased, in contrast to typical cases of diabetic ketoacidosis.

Prescribers should inform patients of signs and symptoms of metabolic acidosis (such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue and sleepiness) and advise them to immediately seek medical advice if they develop such signs and symptoms.

AstraZeneca Limited
347 Parnell Road
Parnell, Auckland 1052
P299 Private Bag 92175, Auckland 1142
New Zealand

Tel + 64 9 306 5650
Fax + 64 9 306 5651

It is recommended that patients taking SGLT2 inhibitors should be assessed for ketoacidosis when they present with signs or symptoms of metabolic acidosis in order to prevent delayed diagnosis and patient management. If ketoacidosis is suspected, treatment with SGLT2 inhibitors should be discontinued. If ketoacidosis is confirmed, appropriate measures should be taken to correct the ketoacidosis and to monitor glucose levels.

Further investigations are being conducted for the risk of diabetic ketoacidosis with SGLT2 inhibitors. Any new advice will be communicated promptly.

Call for reporting

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with these products.

Please contact AstraZeneca on 09 306 5673 or by email Regulatory.NZ@astrazeneca.com to report adverse events. Reports of adverse reactions should also be sent to CARM. Please note that reporting and forms can be downloaded from both the CARM and Medsafe websites https://nzphvc.otago.ac.nz/reporting/ or from www.medsafe.govt.nz/safety/report-a-problem.asp or be obtained by emailing to carmnz@otago.ac.nz or by calling 03 479 7247.

The full prescribing information for Forxiga may be accessed from the Medsafe website at http://www.medsafe.govt.nz/profs/Datasheet/f/forxigatab.pdf

Company contact points

If you have further questions or require additional information, please contact Francisca Reed, Medical Advisor on 09 306 5658 or Gavin Frost, Medical Manager, on 09 306 5673.

Kind regards
AstraZeneca Limited

Gavin Frost
Medical Manager

FORXIGA™ (dapagliflozin 10mg) tablets. Prescription Medicine.
Approved Indication: Forxiga is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated, or for use as combination therapy with other anti-hyperglycaemic agents when these together with diet and exercise do not provide adequate glycaemic control. **Dosage and Administration:** Forxiga 10mg once daily with or without food.**Contraindications:** Known hypersensitivity to any of the ingredients, patients with CrCl <60 mL/min or eGFR persistently <60 mL/min/1.73m^2.**Warnings & Precautions:** Type 1 diabetes, diabetic ketoacidosis, moderate renal impairment, severe hepatic impairment, patients at risk for volume depletion, urinary tract infections, medications known to cause hypoglycaemia, pregnancy and lactation.**Adverse Effects:** Most commonly reported events leading to treatment discontinuation were nausea, dizziness, rash, urinary tract infections and increased creatinine. Adverse reactions reported more commonly than placebo include headache, back pain, genital infection, polyuria, dysuria, dehydration, volume depletion, low blood pressure and blood lipid changes.**Interactions:** Metabolism is primarily mediated by UGT1A9-dependent glucuronide conjugation. Dapagliflozin neither inhibited nor induced CYP enzymes and is not expected to interact with medicines metabolized by these enzymes. Dapagliflozin did not meaningfully inhibit P-gp, OCT2, OAT1 or OAT3 active transporters. Clinically relevant pharmacokinetic effects were not found when dapagliflozin was administered with other diabetes medications.Forxiga is an unfunded Prescription Medicine. A pharmacy charge will apply. For full information please refer to the manufacturers data sheet available at www.medsafe.govt.nz (13 October 2014) before prescribing.
 AstraZeneca Limited, P299 Private Bag 92175, Auckland 1142. Telephone (09) 306 5650 or Facsimile (09) 306 5651.

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AstraZeneca Limited
347 Parnell Road
Parnell, Auckland 1052
P299 Private Bag 92175, Auckland 1142
New Zealand

Tel + 64 9 306 5650
Fax + 64 9 306 5651