STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: FORXIGA
ACTIVE INGREDIENT: Dapagliflozin

Study No: D1692C00015
Forxiga Tablets Specific Clinical Experience Investigation for elderly

Developmental Phase: post-marketing
Study Completion Date: April 2016
Date of Report: August 2016

OBJECTIVES:

The purpose of the investigation is to confirm the following under the post-marketing actual use of Forxiga Tablets (hereinafter referred to as Forxiga) in elderly patients.
-Development of ADRs specified as Key Investigation Items and the risk factors
-Contributing factors possibly having an impact on the safety and efficacy
-Development of ADRs unexpected from the Precautions for use and ADRs under actual drug use

METHODS:

Observational Study\

RESULTS:

Subject population

During the period, 1724 patients were enrolled. Regarding the number of patients whose CRF was collected (fixed number of patients), after 10 patients whose CRF was not collected were excluded, 1st part investigation data (6 months after Forxiga was started) was collected for 1714 patients , and 2nd part investigation data (one year after Forxiga was started) was collected for 1220 patients.

Regarding the 1714 patients with CRF collected (606 institutions), 6 patients in total were excluded: one for contract violation and 5 for no revisit. The remaining 1708 patients were safety evaluable subjects. Among the safety evaluable patients, 16 patients "without

description of efficacy" and 70 patients of "deviation from the approved indications, dosage and administration, etc." were excluded, and the remaining 1622 were considered efficacy evaluable.

Forxiga administration

Administration of Forxiga was continued for "3 months or more" in 1462 patients (85.6%), "6 months or more" in 1272 patients (74.5%), "9 months or more" in 1140 patients (66.7%), and "12 months or more" in 777 patients (45.5%). The number of patients who stopped Forxiga was 653. The most common reason of discontinuation was "Adverse event development" for 169 patients, followed by "Patient's request" for 132 patients, and "No improvement/Aggravated" for 131 patients.
Among the 169 patients who stopped Forxiga due to "Adverse event development", those who stopped the drug "less than 3 months" account for 55.0% (93/169).

Summary of safety results

[1] Adverse drug reaction(ADR)/infection development

ADRs were confirmed in 213 of 1708 safety evaluable patients (12.5%). The cumulative incidence rate of ADR, etc. (hereinafter referred to as ADR incidence rate) in this investigation did not exceed that in domestic clinical studies (17.0%, 172/1012 patients), while comparison between them was difficult due to differences in patient's background, etc.

ADRs with the incidence >/= 0.5% were Pollakiuria in 17 patients (1.0%), Dehydration in 14 patients (0.8%), Pruritus genital in 13 patients (0.8%), Dizziness in 11 patients (0.6%), Rash in 9 patients (0.5%), and Cystitis in 8 patients (0.5%), all of which were expected from the Precautions for Use.

Regarding serious ADRs, 28 events were reported in 18 patients (1.1%). Among them, ADRs developed in 2 patients were Pyelonephritis acute, Cerebral infarction and Ileus. Excepting Pyelonephritis acute, Cerebral infarction and Ileus are unexpected ADRs. However, as there was no evidence suggesting causal relationship between the events and Forxiga, no new action should be taken.

Unexpected ADRs reported for 3 patients or more were Pruritus (7 patients, 0.4%), Glycosylated haemoglobin increased (7 patients, 0.4%), Blood triglycerides increased (5 patients, 0.3%), Diabetes mellitus inadequate control (4 patients, 0.2%), Blood cholesterol increased (4 patients, 0.2%), Low density lipoprotein increased (4 patients, 0.2%), Diabetes mellitus (3 patients, 0.2%), Decreased appetite (3 patients, 0.2%), Cerebral infarction (3 patients, 0.2%), Hypotension (3 patients, 0.2%), and Feeling abnormal (3 patients, 0.2%).

[2] Key investigation item:

In the Risk Management Plan, "Genital infection", "Urinary tract infection", "Hypoglycaemia", "Polyuria,/pollakiuria", and "Adverse events related to volume depletion" are included as important identified risks; " Safety impact of weight loss" is included as important potential risk. Accordingly, in this investigation, the following ADRs were reviewed as key investigation items: ADRs possibly related to genital infection/urinary tract infection, to hypoglycaemia, to polyuria/pollakiuria, to volume deletion, to cardiovascular/cerebrovascular diseases, and to weight decreased. In addition, as there was a concern about skin disorder with SGLT2 inhibitors, ADRs possibly related to skin disorder were also reviewed.

The overall incidence of ADRs possibly related to genital infection/urinary tract infection was 2.3% (39/1708). The incidence rate in female was higher than that in male (3.7% (33/883) vs 0.7% (6/825)). The three patients who had serious ADRs were all female. Serious ADRs were pyelonephritis acute in two patients and urinary tract infection in one patient.

Hypoglycaemia was reported in six patients (0.4%; 6/1708). All patients recovered from the event, and there was no serious case of hypoglycaemia. Four patients out of six patients received concomitant anti-diabetic drug(s).

An ADR which may be related to hypoglycaemia was not reported in the patients who were receiving concomitant drugs which may enhance blood glucose lowering effect at the baseline.

The incidence of ADRs possibly related to pollakiuria/polyuria was 1.2% (20/1708). All events were non-serious ADRs.

The incidences of ADRs sorted by with or without concomitant diuretics at the baseline were: patients without concomitant diuretics 1.1% (17/1551) and patients with concomitant diuretics 2.7% (3/113). All patients with concomitant diuretics were receiving thiazide diuretics.

The incidence of ADRs possibly related to volume deletion was 1.5% (25/1708): dehydration in 14 patients (0.8%), cerebral infarction, hypotension and thirst in three patients each (0.2%), and carotid artery stenosis, transient ischaemic attack, acute myocardial infarction, and angina unstable in one patient each (0.1%). Serious ADRs were reported in five patients: cerebral infarction in two patients, and carotid artery stenosis, acute myocardial infarction, and angina unstable in one patient each.

The incidence of the above ADRs in patients with concomitant diuretics at the baseline was 2.7% (3/113). The rate was higher than those without concomitant diuretics at the baseline (1.4%, 22/1551).

The incidence of the ADRs possibly related to volume deletion was increasing with aging.

The ADRs possibly related to cardiovascular/cerebrovascular diseases were reported in seven patients (0.4%): cerebral infarction in three patients, and transient ischaemic attack, acute myocardial infarction, and angina unstable in one patient each (0.1%). Serious ADRs were reported in five patients: cerebral infarction in two patients, and acute myocardial infarction, angina unstable, and cardiac failure in one patient each.

Six patients were without concomitant diuretics at the baseline.

ADRs possibly related to weight decreased was reported in 5 patients (0.3%). All events were non-serious ADRs.

The numbers of patients with ADRs c possibly related to weight decreased were sorted by BMI: < 18.5 in no patient, 18.5 - < 25 in two patients (0.4%), 25 - < 30 in two patients (0.4%) and 30 in no patient. BMI was unknown in one of five patients with ADRs possibly related to weight decreased.

The incidence of ADRs possibly related to skin disorder caused by FORXIGA was 1.6% (28/1708): rash in nine patients (0.5%), pruritus in seven patients (0.4%) and eczema in four patients (0.2%). All the ADR events were non-serious, and outcomes of the events were either recovered or improving in 25 of 28 patients.

In the patients with skin disorder, five patients were receiving concomitant diuretics at the baseline and four of them were receiving thiazide diuretics.

Summary of efficacy results

In this investigation, HbA1c, fasting blood sugar, random blood sugar, and changes and variations of insulin were reviewed as efficacy indexes of Forxiga. Furthermore, the factors possibly affecting the efficacy were reviewed at the same time: age, weight, baseline BML, baseline serum insulin, baseline blood pressure, and baseline eGFR.

The changes of the efficacy laboratory variables at the time of the final assessment from baseline were as follows: HbA1c -0.44 ± 1.12%; fasting blood glucose level -16.4 ± 55.2 mg/dL; random blood glucose level -16.9 ± 73.0 mg/dL; insulin 1.14 ± 27.76 □U/mL, weight -2.44 ± 2.94 kg; BMI -0.98 ± 1.18 kg/m^2; systolic BP -3.6 ± 15.7 mmHg, and diastolic BP -1.4 ± 10.5 mmHg.

The proportions of the patients who achieved HbA1c reduction at treatment month 12 were as follows: patients who achieved HbA1c < 6.0% in 7.7% (61/791), < 7.0% in 52.1% (412/791) and <8.0% in 84.6% (669/791). All the proportions were higher than the baseline. The proportions increased in all observation periods compared to the baseline.

Concerning the effect of aging, the changes of HbA1c, fasting blood glucose, and random blood glucose from the baseline decreased in the age groups in all observation periods except the random blood glucose level in patients with age 80 or higher. Concerning the effect of concomitant anti-diabetic treatment, HbA1c and random blood glucose level decreased but fasting blood glucose levels did not in patients with concomitant other anti-diabetic treatment compared to those with FORXIGA monotherapy.

Concerning the relationship between the body weight change and HbA1c change at treatment month 12, most patients were distributed in the ranges of HbA1c change (%) < 0 and weight change (kg) < 0 (n=335; 64.7%). There was a trend that the patients commonly had both decreased HbA1c levels and decreased weight after FORXIGA was started.