Forxiga®Tablets
Result of Specific Clinical Experience Investigation on long-term treatment in patients with T2DM (D1692C00014)

1. Summary of Specific Clinical Experience Investigation for long-term use in patients with type 2 diabetes mellitus

The investigation was started in Sep 2014, and collection of CRFs was completed in Aug 2019. The number of enrolled patients was 7793; the number of patients whose CRF was collected was 7712 for CRF1 (3 months after Forxiga was started), 6794 for CRF2 (1 year after Forxiga was started), 5812 for CRF3 (2 years after Forxiga was started), and 5066 for CRF4 (3 years after Forxiga was started).
Regarding the 7712 patients whose CRF was collected, 131 patients in total were excluded: 34 for “contract violation”, 76 for “no revisit after the first visit” and 2 for “not safety evaluated”; the remaining 7581 patients were considered to be safety analysis population. Among the safety analysis population, 2 patients of “out of investigation target”, 15 patients of "without description of efficacy" and 205 patients of "deviation from the approved indications, dosage and administration, etc." were excluded, and the remaining 7359 were considered to be efficacy analysis population.

1.1 Forxiga administration

The duration of treatment in this SCEI was "<3 months" in 670/7581 patients (8.8%), "≥ 3 months and <12 months" in 1049/7581 patients (13.8%), "≥ 12 months and <24 months” in 735/7581 patients (9.7%), "≥ 24 months and <36 months" in 1288/7581 patients (17.0%), "≥ 36 months” in 3838/7581 patients (50.6%) and “not reported” in 1/7581 patient (0%).
The number of patients who stopped Forxiga was 2823/7581 (37.2%). The most common reason for discontinuation was "Changing hospital, no visit during the investigation" for 1137 patients followed by “Patient’s request” for 506 patients, “Adverse event development” for 488 patients, “No improvement/aggravated” for 435 patients, “Others” for 139 patients, “Recovered/improved” for 116 patients, and “Not reported” for 2 patients.

1.2 ADR/infection development

The incidence of adverse reactions(ADRs) in the safety analysis population was 12.9% (981/7581 patients). 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 an ADR incidence rate of ≥ 0.5% were pollakiuria in 70 patients (0.9%), pruritus genital in 51 patients (0.7%), cystitis in 48 patients (0.6%), haematocrit increased in 35 patients (0.5%), and urinary tract infection in 36 patients (0.5%).
Unexpected ADRs with an ADR incidence rate of ≥ 0.3% were blood triglycerides increased in 26 patients (0.3%), hepatic function abnormal in 23 patients (0.3%), and pruritus in 19 patients (0.3%).
Regarding serious ADRs, 167 events were reported in 135 patients (1.8%). Among them, ADRs developed in ≥5 patients were cerebral infarction in 12 patients (0.2%), acute myocardial infarction in 9 patients (0.1%), dehydration in 7 patients (0.1%), angina pectoris in 6 patients (0.1%) and colon cancer in 5 patients (0.1%). All of the ADRs other than dehydration were unexpected.
For these ADRs, no evidence suggesting causal relationship between the events and Forxiga has been obtained. Therefore, no measures such as J-PI revision should be taken.

As stated above, throughout the three-year observation period, there was no new issue concerning the safety profile in this investigation.

1.3 Key investigation item:

In the Risk Management Plan (J-RMP), "Genital infection", "Urinary tract infection", "Hypoglycaemia", "Polyuria,/pollakiuria", "Adverse events related to volume depletion" and “Impact of increased ketones/ketoacidosis” are included as important identified risks; "Safety concerns associated with weight loss", “Renal disorder”, “Liver disorder”, “Fracture”, and “Malignant tumour” are included as important potential risks. 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, to weight decreased, to renal impairment, to hepatic function disorder, to ketone body increase, to malignant tumour, and to bone metabolism. In addition, as there was a concern about skin disorder with SGLT2 inhibitors, ADRs possibly related to skin disorder were also reviewed.
As a result, there is no need to take any new action as all of the ADRs have been included in the Precautions for use of the latest Forxiga package insert to attract attention.

1.4 Efficacy

In this investigation, changes and variations of HbA1c, fasting blood sugar, random blood sugar, insulin, weight, BMI and blood pressure were reviewed as efficacy indexes of Forxiga. Furthermore, the factors possibly affecting the efficacy were reviewed at the same time: age, baseline BML, baseline serum insulin, baseline blood pressure, and baseline eGFR.
As a result, not only blood glucose levels but also other secondary items improved for 36 months, and no particular concerns were observed regarding the efficacy of Forxiga.

As stated above, in the SCEI for long-term use of this drug, no new safety issues were identified, and there are no concerns about its efficacy, and there should be no need to take any specific action.