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Forxiga®Tablets
Protocol of SCEI for long-term use

1. Purpose of the investigation:

The purpose of the investigation is to confirm the following under the post-marketing actual use of Forxiga Tablets (hereinafter referred to as Forxiga).

-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

2. Target number of patients and the rationale

Target number of patients: 3000 evaluable patients for 3 years (number of patients of analysis target)

Rationale: The probability in which more than one event of the ADR with the true frequency of 0.1 % or more is reported is 95%, so the number of evaluable patients for 3 years is set at 3000.

Among the 728 patients receiving the study drug (monotherapy: 249, combination therapy: 479), 98 patients (monotherapy: 28, combination therapy: 70) were withdrawn from the study. The rate of withdrawal was 13.5%. Considering that the observation period of 3 years is longer compared to the clinical studies, the rate of withdrawal for one year is assumed as 20%. Assuming that about 20% of patients would withdraw from the investigation per year, 6000 patients should be needed to obtain 3000 evaluable patients for 3 years.

3. Subject of the investigation

Patients treated with Forxiga for the first time due to type 2 diabetes mellitus, which is the indication of the drug.

4. Observation period

3 years

Rationale: It is expected that Forxiga will be used for a long term under actual drug use, which may cause a burden on medical professionals. The observation period was decided as 3 years based on the feasibility taking into account the burden on medical professionals. The studies of other anti-diabetic agents were conducted also with the observation period of three years. Therefore, it was considered that bibliographic consideration could be made compared with the results of the studies.

5. Number of investigation centres (by category of department)

About 1200 medical institutions providing treatment for diabetes mellitus (mainly department for metabolic/endocrine disorders and diabetes internal medicine department)

6. Investigation method

(1) Target investigation medical institutions are hospitals where Forxiga has been delivered and started to be used. Medical Representatives (hereinafter referred to as MRs) will explain the objectives, target and method of the investigation to physicians of the hospitals who will conduct the investigation, and will request the investigation to the head of the hospital (hospital director, etc). Written contract must be concluded prior to the start of the SCEI.

(2) The investigation method should be central registration method. The method of collecting the data should be EDC (Electronic Data Capture) via Internet in principle. For the institutions where EDC is not available, paper CRF should be prepared, and after the conclusion of contract, MR in charge should distribute Case Registration Form and CRF to the investigator.

(3) The investigator should enter the required information on the registration screen of EDC to enrol the patient within 14 days after the drug is started in the patient defined as '3. Subject of the investigation' as the above (the start date should be Day 1). In the case of institutions where paper CRF should be used, the investigator should fill in the Case Registration form and sent it to the registration centre by fax within 14 days after the drug is started in the patient (the start date should be Day 1).

(4) The investigator monitors the patient according to '4. Observation period', enter the data on the screen of EDC as needed for all enrolled patients, and put an electric signature. In the case of institutions where paper CRF should be used, the investigator should fill in the CRF within around 6 weeks after the observation period, and hands it to the MR in charge.

The study data input will be performed three times: 3 month after the drug was started (1st part study data), 1 year after the drug was started (2nd part study data), 2 years after the drug was started (3rd part study data), 3 years after the drug was started (4th part study data).

7. Investigation period

Registration period: September 2014 (the next month after 3 months from the launch) - August 2016
Investigation period: September 2014 (the next month after 3 months from the launch) – April 2020
However, enrolment will not be accepted when the target number of patients is considered to be achieved by the number of enrolled patients.

8. Data items, etc.

(1) Patient demography

Identity number (patient number), date of birth or age, sex, indication of Forxiga, duration of diabetes mellitus, inpatient/outpatient, smoking history, drinking habit, allergy, previous treatment of diabetes mellitus (the drug used within four weeks prior to the initiation of Forxiga and diet therapy just before the initiation of Forxiga) (if with, the name of the drug and the administration route), HbA1c, fasting blood sugar, random blood sugar

(2) Physical findings, observation items (weight, blood pressure, pulse rate,diet therapy and exercise therapy)

Height, weight, BMI (calculated based on height and weight), blood pressure, pulse rate, diet therapy and exercise therapy (details and compliance)

(3) Past medical history/concomitant disease

with/without past history/complication (if with, the disease such as hypertension, malignant tumour, cardiovascular/cerebrovascular disease, urinary tract infection, genital infection, osteoporosis, dyslipidemia, gout, and hyperuricemia), the severity of concurrent renal disorder/hepatic disorder if it exists, the severity of past/concurrent cardiac failure if it exists (NYHA cardiac function classification), with/without diabetic complication (if with, nerve disorder, nephropathy, or retinopathy)

The criteria for severity assessment of renal disorder and liver disorder are as follows:

-The criteria for severity assessment in patients with renal impairment

eGFR（mL/min/1.73m^2）>= 90 based on the value calculated from age, sex and the serum creatinine: normal; >= 60 and < 90: mild (mild impairment); >= 30 and < 60: moderate (moderate impairment); < 30: severe (severe impairment). (Ref. Table 5 Frequency of CKD severity classification in patients underwent specific health examination of Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012)

-The criteria for severity assessment in patients with hepatic function disorder

Regarding the criteria for severity assessment in patients with hepatic function disorder, severity assessment by the investigator (mild [mild impairment], moderate [moderate impairment], severe [severe impairment]) is prioritized since a uniform criteria using the upper limit of the site reference range may not reflect the individual patient's condition. The investigator should enter the severity criteria as the result of comprehensive assessment of the patient's condition and laboratory values, using Child-Pugh classification, etc as a reference.

(4) Forxiga administration

Start date of Forxiga, dose, daily frequency of administration, administration timing (morning, lunch time, evening, etc.); when the dose was changed, the dose after the change, date of the dose change, and the reason of the dose change.

(5) Whether Forxiga was continued or stopped

treatment continued/discontinued (the last administration date if treatment was continued, the stop date and the reason for withdrawal if treatment was discontinued)

(6) Dosage and administration of concomitant drug(s)

With/without concomitant drug(s) during treatment with Forxiga (if with, the drug name, administration route, indication, and treatment duration; in patients receiving antidiabetic drugs or diuretics concomitantly and patients experienced AEs, daily dose (unit) and daily frequency of administration in addition to the above items).

(7) With/without pregnancy or lactation during the observation period

With/without pregnancy or lactation during the observation period (expected delivery date or lactational period if pregnancy or lactation was confirmed)

(8) Laboratory test data

If any laboratory test described below was performed under daily practices, the date of measurement or test and the value should be described in the CRF.

[Laboratory test item]

Fasting blood sugar, random blood sugar, HbA1c (NGSP), insulin, serum creatinine, eGFR, BUN, AST, ALT, gamma-GTP, ALP, total bilirubin, blood lipid (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride), uric acid, haemoglobin, haematocrit, serum albumin, Na, Cl, K, Ca, P, Mg, serum ketone body, urinalysis qualitative (ketone body, protein, uric blood, urinary sediment), urinalysis quantitative (creatinine, albumin [creatinine correction])

(9) Handling of serious adverse events (SAEs)

If any SAE developed (see '10) Adverse Events and Abnormal laboratory values associated with AE'), the investigator should enter the information into EDC promptly. Even if the event was not serious, the data should be entered into EDC as promptly as possible.

(10) Adverse events and abnormal laboratory values concerning adverse events

With/without Adverse event (if with, the AE term, onset date, seriousness, causality with Forxiga, outcome, outcome date, with/without change of administration of Forxiga, with/without treatment for the AE, with/without alternative contributing factor, change of related laboratory test values; in case of SAE, the clinical course should be reported in addition to these items).

Adverse event is:

Defined as every unfavourable medical event newly developed or aggravation of the pre-existing medical condition in the patient received a drug, whether or not considered as related to the drug. Therefore, regardless the causality with administration of the drug, all undesirable or unintended signs (including abnormal clinical laboratory tests), symptoms, and disease should be handled as AE. AEs can be obtained by spontaneous reporting by patients, medical interview, clinical

examinations, or clinical evaluation.

The investigator should enter the data into EDC promptly according to the AE reporting method also in the following cases:

-Pregnancy

-Overdose[1]

-Carcinoma

Serious Adverse Event is:

All undesirable medical events among AEs described below (regardless the dose).

-Patient died (death)

-Life-threatening (which may result in fatal outcome)[2]

-Involved or prolonged inpatient hospitalization is required for treatment (involved or prolonged inpatient hospitalization)[3]

-Involved persistence or significant disability or incapacity (disability)

-Congenital anomaly/birth defects (congenital disorder or anomaly in later generations)

-Other medically important condition (serious other than death, life threatening, involved or prolonged inpatient hospitalisation, and disability)[4]

Causal relationship between AEs and Drug

-Yes (probable): the causality with Forxiga cannot be excluded.

-Yes (possible): the causality with Forxiga cannot be excluded.

-No (deniable): the causality with Forxiga can be excluded.

Outcome of AE

-Recovered: AE disappeared or the condition returned to that before the initiation of the drug.

-Recovering: AE improved but the sign/symptom still persists.

-Not recovered: The symptoms of the AE persisted or were aggravated, including the cases in which the symptoms persisted until the patient died.

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[1] In case that an excessive and clinically significant dose of the drug was administered inadvertently or intentionally.

[2] It means the case in which the patient was at risk of death at the onset of the AE. It should not be assumption that the patient might die if the event was more serious.

[3] The following cases are not 'Involved or prolonged inpatient hospitalization'.

-Stay in the ER or the emergency department less than 24 hours, which did not result in hospitalization (However, if it was due to the medically important or life-threatening event, the corresponding serious criterion should be selected).

-Hospitalisation for treatment which was scheduled prior to the initiation of Forxiga

-Hospitalisation not for treatment of the disease (scheduled prior to the initiation of Forxiga, such as hospitalisation for examinations not requiring treatment with bed rest)

-Hospitalisation due to other living conditions not requiring medical therapy/surgical procedure, regardless the health condition (monitoring not requiring treatment with bed rest, difficulty in hospital visit due to housing environment, request by the patient/patient's family, economic difficulties, administrative reasons, etc.)

[4] Important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. It should be decided on the medical and scientific basis. Examples of such events are intensive treatment in an emergency room or at home for allergic

bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation, but are not limited to.

-Recovered with sequelae (sequelae): The AE itself disappeared or the condition returned to that before the initiation of the drug, however, disabling dysfunction remained.

-Death (death from the AE): The patient died of the AE.

Unknown: It is difficult to confirm the outcome because of changing hospital, no visit, etc.

(11) Rationale and practical investigation method for key investigation items

AEs related to genital infection/urinary tract infection, hypoglycaemia, pollakiuria/polyuria, volume depletion (dehydration, cardiovascular risks including thrombosis/embolism such as cerebral infarction), weight decreased, renal disorder, and ketone bodies increased; malignant tumour (especially bladder cancer and breast cancer); influence on bone metabolism.

Rationale: As these are concerned after administration of Forxiga, the pattern of these AEs, etc should be examined.

Investigation method: The above mentioned events, etc. should be described clearly as 'Key Investigation Item' with the case examples in the section of adverse event of CRF (EDC screen) and the implementation guideline. It is instructed to fill the Adverse event section without fail if any of these events, etc. occurred.

<Observation schedule>

	CRF (EDC data entry)						
	1st part study data			2nd part study data		3nd part study data	4th part study data
	Start of treatment	1 month	3 months	6 months	1 year	2 years	End of the observation period of 3 year** or at the time of discontinuation of Forxiga***
Patient demography	○						
Forxiga administration	←	—	—	—	—	—	→
Dosage and administration of concomitant drug(s)	←	—	—	—	—	—	→

Clinical course -HbA1c, fasting blood sugar, random blood sugar, weight -Blood pressure, pulse rate, insulin, serum creatinine, eGFR, BUN, AST, ALT, gamma-GTP, ALP, total bilirubin, blood lipid, uric acid, haemoglobin, haematocrit, serum albumin, Na, Cl, K, Ca, P, Mg, serum ketone body, urine analysis, etc,	○*	○	○	○	○	○	○
	○*	○	○	○	○	○	○
Adverse event	←						→

* The data of the closest date to the initiation of Forxiga should be entered.

** End of the observation period should be the closest date to the termination date within the period of 4 weeks before or after the termination date. If the patient did not visit during the period of 4 weeks be fore and after the termination date of the observation period, the end of observation period should be the date of last visit before the termination date.

*** The time of discontinuation of Forxiga should be the date of the last visit during the treatment or the next day of the last administration of Forxiga.

9. Items and method for analysis

Further details about conditions of target populations and analysis method are included in the statistical analysis plan.

(1) Items about structure of patients to analyse

Number of enrolled patients, number of patients whose CRF was collected, number of safety evaluable patients, number of efficacy evaluable patients, number of patients to exclude and the reason for exclusion

(2) Items about patient demography

Age, sex, inpatient/outpatient, BMI, smoking history, drinking habit, duration of illness from the first onset, allergy, past history, concomitant disease (liver disorder, renal disorder, cardiac failure, others), eGFR, previous diabetic drugs, HbA1c, fasting blood sugar, random blood sugar

The value of eGFR should be calculated by the formula below.

eGFR (mL/min/1.73 m^2) = $194 \times (SCr)^{-1.094} \times (age)^{-0.287}$ ($\times$ 0.739 if female)

(3) Items about treatment

Dose, daily dose, concomitant drug (with/without, the type), concomitant therapy (with/without, the type)

(4) Safety items

1) ADR/infection development by category
2) ADR/infection development by patient demographic factor and by treatment
ADR/infection development by patient demographic factor and by treatment should be confirmed to review factors affecting the safety of Forxiga.
3) Development of SAE by category
4) Development of Key Investigation Items

(5) Efficacy items
1) Mean variations of HbA1c and fasting blood sugar from the baseline values
2) Achievement rate of HbA1c to <6.0%(NGSP), <7.0 % (NGSP), and <8.0% (NGSP).
3) Mean variations of weight and blood pressure from the baseline values
4) Changes of HbA1c, fasting blood sugar, weight, and BMI.

(6) Items concerning patients with special background
1) Safety and efficacy in patients with renal impairment, patients with hepatic function disorder, and elderly patients
2) Safety in patients with cardiac failure

(7) Others
1) Information about concomitant drugs (drug name, dosage and administration) and the safety in concomitant use of them and Forxiga
2) Influences by concomitant use with diuretics, with drugs for treatment of gout or hyperuricaemia, and with drugs for treatment of osteoporosis (regardless of AE development)
3) Influence of excessive weight decrease on the safety (especially in low-weight patients)
4) Relationship between weight and HbA1c
5) Safety and efficacy in concomitant use with insulin

10. Organisation to conduct the investigation

The organisation to conduct the investigation is the same as that in the attachment 2) to the Risk Management Plan.

11. In case of entrusting investigational operation partially, the name and address of the contractor and the entrusted operations

Contract partners

Address: [redacted]

Name: [redacted]

Entrusted operations: [redacted]

[redacted]

Request to and contract with medical institutions, promotion of case registration, collection of CRFs and follow-up investigation, etc.

Address: [redacted]

Name: [redacted]

Entrusted operations: [redacted]

[redacted]

12. Other necessary items

(1) Amendment of the protocol

During the investigation period, the number of withdrawal, development of unexpected serious ADRs, remarkable increase of incidence of specific ADRs, and validity of investigation items should be grasped continuously based on the Risk Management Plan. If needed, the protocol should be reviewed and revised.

In case of s-NDA is approved for dosage and administration or indications during the investigation period of this drug (except the case when the re-examination period is established newly), the protocol should be reviewed and revised appropriately.

(2) Actions when issues/questions are recognized

Conduct of Specific Clinical Experience Investigation and Post-marketing Clinical Studies is to be examined to detect/confirm their factors and to verify discussion outcome in following conditions based on the Risk Management Plan: when development of a significant ADR unexpected from the Precautions for use is suggested, when the frequency of an ADR is excessively increased, when an issue was recognized in safety and efficacy compared to their condition before launch, and when development of a different kind of ADR is suggested.

(3) Presentation of data

Regarding this investigation, we will present data concerning specified items of all enrolled patients (including those with data at enrolment only) on regular basis (1 year and 2 years after

the start of investigation, and at the end of investigation).

○ Attachment

A. Contract template (draft)

B. Specific Clinical Experience Investigation guidance (draft)

C. Specific Clinical Experience Investigation Case Registration Form (draft)

D. Specific Clinical Experience Investigation CRF (draft)