

Forxiga®Tablets
Protocol of SCEI for elderly

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) 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

2 . Target number of patients and the rationale

All of elderly patients treated with Forxiga for the first time (65 years and above) during three months after the launch are to be enrolled as much as possible. The patients to be investigated are those who started Forxiga, regardless the date of contract.

3 . Subject of the investigation

Patients treated with Forxiga for the first time during three months after the launch due to type 2 diabetes mellitus, which is the indication of the drug, aged 65 or over at the time when Forxiga was started.

In addition, patients receiving the study drug of Forxiga before the launch should be included also.

4 . Observation period

1 year

Rationale: The observation period was determined as one year based on the 'Guideline for Clinical Evaluation of Oral Hypoglycemic Agent' and to see the environmental influence such as seasons. In addition, the Japanese Study D1692C00012 was conducted also with the observation period of one year. Bibliographic consideration will be made compared with the result of the study.

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

Medical institutions providing treatment for diabetes mellitus (mainly department for endocrine/metabolic disorders and diabetes internal medicine department) where the drug was adopted and delivered within 3 months after the launch and a contract was made according to '6. Investigational method'.

In addition, medical institutions where the study drug of Forxiga was used before the launch should be included also.

6. Investigation method

- (1) AZKK Medical Representatives (MRs) explain objectives, target patients and methods of this SCEI to the physicians in charge of the SCEI at the medical institutions which decided to issue prescriptions of Forxiga and where '3. Subject of investigation' is confirmed, and request conduct of the SCEI to the head of the medical institution. 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.
- (3) The investigator should enter the required information on the registration screen of EDC to enrol the patient defined as '3. Subject of the investigation' as the above. To enrol retrospectively the patient who is receiving Forxiga already at the time of concluding a contract, the investigator should enter the required information on the registration screen of EDC as promptly as possible.
- (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.
The study data input should be performed twice: 6 months after the drug was started (1st part study data) and 1 year after the drug was started (2nd part study data).

7. Investigation period

Registration period: Elderly patients started Forxiga within 3 months after the launch will be enrolled comprehensively.

Investigation period: September 2014 (the next month after 3 months from the launch) - April 2016

In addition, patients receiving the study drug of Forxiga before the launch should be also included.

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 name such as hypertension, malignant tumour, cardiovascular/cerebrovascular disease, urinary tract infection, genital infection, osteoporosis, dyslipidaemia, 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/1.73m²) \geq 90 based on the value calculated from age, sex and the serum creatinine: normal; \geq 60 and $<$ 90: mild (mild impairment); \geq 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) 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])

(8) Handling of serious adverse events (SAEs)

If any SAE developed (see '9) 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.

(9) 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
- Overdose¹
- 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

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

- 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.
- 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.

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

Development of AEs related to genital infection/urinary tract infection, hypoglycaemia, pollakiuria/polyuria, volume depletion (dehydration, cardiovascular risks including thrombosis/embolism such as cerebral infarction), and weight decreased.

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

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.

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	
	Start of treatment	1 month	3 months	6 months	9 months	End of the observation period of 12 months (1 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 before 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.

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

(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 and patients with hepatic function disorder

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.

- 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)