STUDY REPORT SYNOPSIS

XIGDUO XR (DAPAGLIFLOZIN/METFORMIN XR FDC)

Regulatory Postmarketing Surveillance

Milestones:	Date of Fist Subject In: 20 Apr 2017 Date of Last Subject Last Visit: 30 Aug 2019
Phase of development:	Not Applicable – Observational study
Sponsor:	AstraZeneca Korea Ltd.

Background/rationale:

As part of a post approval commitment, the MFDS has requested a postmarketing surveillance program to characterize safety in patients who are treated with Xigduo XR for T2DM by physicians in the normal clinical practice setting. This study is designed to confirm assess the known safety profile or identify previously unsuspected adverse reactions and to evaluate the effectiveness of Xigduo XR under conditions of routine daily medical practice in Korea.

This study provides information on the Korean patient population that is treated with this drug.

Objectives:

The primary objective of this study is :

Descriptive analysis of the percentage (%) of adverse events (AEs), serious adverse events (SAEs), unexpected adverse events·adverse drug reactions and AEs of special interest (AESI) in patients who are treated with Xigduo XR for type 2 diabetes mellitus by physicians in the normal clinical practice setting over a period of 12 and 24 weeks.

The secondary objectives of this study are:

To follow the changes of the hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), 2-hr post-prandial glucose (PPG-2hr), blood pressure, abdominal circumference and body weight and self-reported data in this cohort of patients from baseline to completion of the study.

To evaluate the safety and tolerability of Xigduo XR in patients with type 2 diabetes mellitus based on conducted laboratory test. (Laboratory tests are not mandatory because of the non-interventional nature of this study)

Study design:

This is a local, prospective, non-interventional, regulatory postmarketing surveillance study. Adult patients with type 2 diabetes mellitus who are initiating Xigduo XR as indicated by the MFDS are included. 600 patients are followed up 12 weeks and at least 60 patients of the 600 patients are followed up 24 weeks. Patients were treated as part of routine practice at Korean healthcare centers by accredited physicians. In this study, patients received Xigduo XR in conjunction with diet and exercise modifications for the treatment of T2DM.

Data source:

Only medical institutions licensed by Regulatory Authorities can be included to the study. AstraZeneca made a selection of relevant departments, such as internal medicine, family medicine, and other appropriate department which can offer DM control medical services of university hospitals, general hospitals and clinics where the surveillance drug is mainly prescribed and where staff can sufficiently fulfill the objectives of the surveillance and start for surveillance after signing a written contract. Patients' medical records are data sources in this study. Only if the laboratory test is done as part of standard of care practice is the data be collected for this study as per decision of the investigator.

Study population:

Adult patients who are diagnosed with T2DM eligible for the treatment with Xigduo XR according to prescription information approved by MFDS and as decided by the investigator

Inclusion criteria:

1. Patients aged 18 years and older

2. Patients with T2DM eligible for treatment with Xigduo XR at first according to the indication as indicated in the locally approved prescribing information

3. Patients with evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Exclusion criteria:

1. Hypersensitivity to the active substances or to any of the excipients

2. Patients with renal impairment (e.g., serum creatinine levels ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women, or creatinine clearance < 60 ml/min or eGFR< 60mL/min/1.73 m2) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.

3. Patients with type 1 diabetes mellitus, lactic acidosis, or acute or chronic metabolic acidosis including diabetic ketoacidosis with or without a coma

4. Diabetic precoma

5. Congestive heart failure that medicinal treatment is required

6. Patients with radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials)

7. Patients with severe infection or severe traumatism

8. In terms of Surgical procedures (except minor procedures not associated with restricted intake of food and fluids)

9. Patients with nutrition poor condition, starvation condition, pituitary insufficiency, capsular insufficiency

10. Patients with impaired hepatic function (Since impaired hepatic function has been associated with some cases of lactic acidosis, this drug should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.), respiratory failure, acute myocardial infarction, acute or chronic disease causing histotoxic hypoxia like shock, an alcoholic, gastroenteric trouble (anhydremia, diarrhea, vomiting and etc.)

11. Pregnant women, women with potential of pregnancy, lactating women

12. Patients with hereditary problems such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Statistical methods:

Statistical analyses are of descriptive nature.

All analyses were performed for the total study population which consists of all patients taking at least one dose of Xigduo XR.

All excluded data (including patients who take the study drug for unauthorized indication) from analyses are reported separately on the post-marketing surveillance report.

Results:

Overall participation status

From 29 May 2015 to 25 Nov 2019, CRFs were retrieved from 797 subjects by 27 investigators at 24 study sites. Among the subjects who retrieved CRFs, 623 subjects were included in the safety analysis set, excluding 31 subjects who have taken Xigduo prior to the contract date, 1 subject who have not taken Xigduo, 2 subjects for follow-up failure, 140 subjects who have been violated the inclusion/exclusion criteria. From the safety analysis set, 564 subjects were included in the effectiveness analysis set, excluding 42 subjects whose final effectiveness assessment after last visit was “assessment impossible”, 2 subjects who administered only Dapagliflozin between administration first date and effectiveness assessment date, and 15 subjects whose HbA1c, FPG, PPG-2hr, blood pressure, weight, and waist circumference differences were all not calculated at visit 1 and visit 2 compared to baseline. Of these, 243 subjects who administered Xigduo more than 24 weeks or more were classified as long-term subjects.

Descriptive data

Sex: Among the 623 subjects in the safety analysis set, 61.64% (384/623 subjects) were male and 38.36% (239/623 subjects) were female.

Age: The mean age of the subjects was 55.15±11.47 years. The distribution of age groups showed 30.66%(191/623 subjects) for '60 years ~ 69 years', 30.50%(190/623 subjects) for '50 years ~ 59 years', 20.71%(129/623 subjects) for '40 years ~ 49 years', 9.79%(61/623 subjects) for '< 40 years', and 8.35%(52/623 subjects) for '≥ 70 years'.

Pediatrics (< 19 years of age): When '< 19 years of age' is classified as a pediatric group, there were no pediatric subject.

Geriatrics (≥ 65 years of age): In total, 21.35% (133/623 subjects) were geriatric subjects, defined as those at or above 65 years of age.

Pregnant women: During this re-examination surveillance period, no data on pregnant women was collected.

Breast feeding women: During this re-examination surveillance period, no data on breast feeding women was collected.

Height: Excluding 64 subjects whose height information was not collected, the mean height of 559 subjects was 165.58±9.12 cm, raging from minimum 141.00 cm to maximum 187.00 cm.

Body weight: Excluding 115 subjects whose body weight information was not collected, the mean body weight of 508 subjects was 75.35±14.43 kg, raging from minimum 35.00 kg to maximum 133.70 kg.

Waist circumference: Excluding 494 subjects whose waist circumference information was not collected, the mean waist circumference of 129 subjects was 94.96±9.70 cm, raging from minimum 66.00 cm to maximum 127.00 cm.

BMI: Excluding 144 subjects whose height or body weight information was not collected, the mean BMI of 479 subjects was 27.41±3.88 kg/m2, ranging from minimum 16.60 kg/m2 to maximum 46.00 kg/m2. BMI < 25 kg/m2 made up 25.68% (123/479 subjects) and subjects with BMI ≥ 25 kg/m2 made up 74.32% (356/479 subjects).

Serum creatinine: Excluding 7 subjects whose Serum creatinine was not collected, the mean serum creatinine of 616 subjects was 0.82±0.18 mg/dl, ranging from minimum 0.35 mg/dl to maximum 1.35 mg/dl.

eGFR: Excluding 7 subjects whose eGFR information was not collected, the mean eGFR of 616 subjects was 93.74±15.18 ml/min/1.73m2, ranging from minimum 60.00 ml/min/1.73m2 to maximum 139.70 ml/min/1.73m2.

Blood pressure: Excluding 105 subjects whose blood pressure information was not collected, the mean systolic blood pressure of 518 subjects was 127.93±14.46 mmHg, raging from minimum 90.00 mmHg to maximum 184.00 mmHg. The mean diastolic blood pressure was 76.65±11.14 mmHg, raging from minimum 47.00 mmHg to maximum 130.00 mmHg.

Duration of T2DM: Excluding 312 subjects whose duration of disease information was not collected, the mean duration of T2DM of 311 subjects was 46.86±54.93 months, ranging from minimum 0.03 month to maximum 298.94 months. The distribution of disease duration of 560 subjects who were available for categorical analysis with collected date showed '1 year ~ < 4 years' in 26.25% (147/560 subjects), '< 1 year' in 24.46% (137/560 subjects), '4 years ~ < 8 years' in 20.71% (116/560 subjects), '≥ 12 years' in 17.32% (97/560 subjects), and '8 years ~ < 12 years' in 11.25% (63/560 subjects).

Past medical history: In total, 16.05% (100/623 subjects) of subjects had past medical history. Analyzing the past medical history by System Organ Class (SOC) with overlapped counting, the results showed 'Infections and infestations' in 22.00% (22/100 subjects), 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' in 16.00% (16/100 subjects), and 'Gastrointestinal disorders' in 13.00% (13/100 subjects).

Present medical history: In total, 93.26% (581/623 subjects) of subjects had present medical history. Analyzing the present medical history by system organ class (SOC) with overlapped counting, the results showed 'Metabolism and nutrition disorders' in 75.22% (437/581 subjects), 'Vascular disorders' in 61.62% (358/581 subjects), and 'Nervous system disorders' in 22.89% (133/581 subjects).

Family history of diabetes mellitus: In total, 27.61% (172/623 subjects) of subjects had family history of diabetes mellitus.

Diabetes complications: In total, 19.42% (121/623 subjects) of subjects had diabetes complications.

Renal impairment: In total, 1.12% (7/623 subjects) of subjects had renal impairment. The severity of renal impairment was classfied as 'Mild', 'Moderate or Severe', and 'Severe or End-stage renal disease requiring hemodialysis' for analysis. The severity of renal impairment was 'Mild' in all subjects.

Hepatic impairment: In total, 13.16% (82/623 subjects) of subjects had hepatic impairment. The severity of renal impairment was classfied as 'Mild', 'Moderate', and 'Severe' for analysis. The severity of 82 subjects was 'Mild' in 98.78% (81/82 subjects), 'Moderate' in 1.22% (1/82 subjects).

Total administration period of Xigduo XR: The mean total administration period of Xigduo XR was 154.72±73.25 days, ranging from minimum 2 day to maximum 422 days. The distribution of total administration period showed '< 12 weeks ~ < 24 weeks' in 54.37% (336/618 subjects), '≥ 24 weeks' in 40.45% (250/618 subjects), and '<12 weeks' in 5.18% (32/618 subjects).

Total administration dose of Xigduo XR (Dapagliflozin): The mean total administration dose of Xigduo XR (Dapagliflozin) was 1,547.23±732.55 mg, ranging from minimum 20.00 mg to maximum 4,220.00 mg.

Total administration dose of Xigduo XR (Metformin): The mean total administration dose of Xigduo XR (Metformin) was 130,620.75±72,919.18 mg, ranging from minimum 1,000.00 mg to maximum 422,000.00 mg.

Discontinuation of Xigduo XR administration: In total, 5.14% (32/623 subjects) of subjects discontinued Xigduo XR administration within 12 weeks from the initiation of Xigduo XR. The reason for discontinuation was 'Stop visit', 'Adverse Event' in 34.38% (11/32 subjects), and 'Others' in 31.25% (10/32 subjects)

Other anti-diabetic agent: In total, 87.80% (547/623 subjects) of subjects received anti-diabetic agents other than Xigduo XR.

Concomitant medications: In total, 88.76% (553/623 subjects) of subjects received concomitant medications other than anti-diabetic agents. Analyzing the types of concomitant medications other than anti-diabetic agents with overlapped counting, they included 'Dyslipidaemic Agents' in 73.42% (406/553 subjects), 'Anticoagulants, Antiplatelets & Fibrinolytics (Thrombolytics)' in 34.18% (189/553 subjects), and 'Other Antihypertensives' in 26.94% (149/553 subjects)

Long-term users: Analyzing 618 subjects excluding 5 subjects whose administration period of Xigduo XR was not collected, 40.45% (250/618 subjects) of subjects were long-term users, defined as those who had taken Xigduo XR for more than 24 weeks.

Safety data

During this re-examination surveillance period, 113 adverse events were reported from 89 subjects out of 623 subjects in the safety analysis set. Thus, the overall incidence rate was 14.29% (89/623 subjects). The most common adverse events by system organ class (SOC) included 'Gastrointestinal disorders' in 2.73% (17/623 subjects), 'Nervous system disorders' in 2.25% (14/623 subjects), and 'Infections and infestations' in 2.09% (13/623 subjects). The most common adverse events by preferred term (PT) included 'Dizziness' in 1.12% (7/623 subjects), 'Constipation' in 0.80% (5/623 subjects), and 'Abdominal pain upper', 'Dyspepsia', 'Vaginal infection' in 0.48% (3/623 subjects). Among these, incidence rate of adverse drug reactions for which causal relationship to Xigduo XR could not be excluded was 6.26% (39/623 subjects, 42 cases). The most common adverse drug reactions by SOC included 'Gastrointestinal disorders' in 1.61% (10/623 subjects), 'Nervous system disorders' in 1.12% (7/623 subjects), and 'Investigations', 'Reproductive system and breast disorders' in 0.64% (4/623 subjects). The most common adverse drug reactions by PT included 'Dizziness', 'Constipation' in 0.64% (4/623 subjects), 'Abdominal pain upper', 'Vaginal infection', 'Hypoglycaemia' in 0.32% (2/623 subjects), 'Pruritus', 'Abdominal discomfort', 'Diarrhoea' in 0.16% (1/623 subject).

During the surveillance period, incidence rate of serious adverse events was 1.93% (12/623 subjects, 13 cases). The most common serious adverse events by SOC included 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)' in 0.48% (3/623 subjects), 'Infections and infestations', 'Injury, poisoning and procedural complications' in 0.32% (2/623 subjects), 'Nervous system disorders', 'Musculoskeletal and connective tissue disorders', 'General disorders and administration site conditions' in 0.16% (1/623 subject). The most common unexpected adverse events by PT included 'Guillain-Barre syndrome', 'Pneumonia bacterial', 'Sialoadenitis' in 0.16% (1/623 subject). Among these, incidence rate of serious adverse drug reactions for which causal relationship to Xigduo XR could not be excluded was 0.16% (1/623 subject, 1 case). Serious adverse drug reaction was 'Cholecystitis acute' of “Hepatobiliary disorders”.

Efficacy data

Analayzing the results of final effectiveness assessment in the effectiveness analysis set, 78.72% (444/564 subjects) was 'Improved', 15.07% (85/564 subjects) was 'Unchanged', and 6.21% (35/564 subjects) was 'Worsened'. Results of final effectiveness assessment were also categorized as “Effectiveness” which included 'Improved' and “Ineffectiveness” which included 'Unchanged' and 'Worsened'. The results showed 78.72% (444/564 subjects) was 'Effectiveness' and 21.28% (120/564 subjects) was 'Ineffectiveness'.

Conclusion: In conclusion, the existing favorable benefit-risk balance of Xigduo is confirmed to be remained through the post-marketing surveillance, and AstraZeneca will continue to conducting pharmacovigilance and assess the safety of Xigduo in accordance with domestic and foreign regulations in order to monitor the safety of Xigduo.