Proposed packaging material		
Code	XIGDUO XR 5/500; 5/1000; 10/500; 10/1000 mg-PI-03.04	
Regulatory Objectives	☐ NDA ☐ Renewal ☒ Variation change detail no.: RO-Change Event-0036591	
Code of previous version	XIGDUO XR 5/500; 5/1000; 10/500; 10/1000 mg-PI-02.01	
Changes	XIGDUO XR 5/500 5/1000 10/500 10/1000 mg – Wider Indication	
Reference	☐ CDS version: ☐ CPIL version:	☐ SmPC country/version/date: ☐ GRL approval:
Name	MNAI	

XIGDUO XR™ XR
5/500; 5/1000; 10/500; 10/1000 mg
(dapagliflozin/metformin HCl extended release)
Extended Release Film-coated Tablet

Qualitative and quantitative composition

XIGDUO XR is available for oral administration as extended release film-coated tablets containing dapagliflozin and metformin hydrochloride as following quantitative composition:

- XIGDUO XR 5/500 mg: Each film-coated tablet contains 5 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin HCl extended-release
- XIGDUO XR 5/1000 mg: Each film-coated tablet contains 5 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin HCl extended-release
- XIGDUO XR 10/500 mg: Each film-coated tablet contains 10 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin HCl extended-release
- XIGDUO XR 10/1000 mg: Each film-coated tablet contains 10 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin HCl extended-release

Pharmaceutical form

XIGDUO XR is a combination of dapagliflozin and metformin HCl extended-release.
XIGDUO XR tablets are available in the following dosage forms and strengths:

- 5 mg/500 mg tablets are orange, capsule shaped, film-coated tablets debossed with “1070” and “5/500” on one side and plain on the other side.
- 5 mg/1000 mg tablets are pink to dark pink, biconvex, oval shaped, film coated tablets debossed with “1071” and “5/1000” on one side and plain on the other side.
- 10 mg/500 mg tablets are pink, biconvex, capsule shaped, film-coated tablets debossed with “1072” and “10/500” on one side and plain on the other side.
- 10 mg/1000 mg tablets are yellow to dark yellow, biconvex, oval-shaped, and film-coated tablets with "1073" and "10/1000" debossed on one side and plain on the reverse side.

Therapeutic indication

XIGDUO XR (dapagliflozin and metformin HCl extended-release) is indicated in adult patient type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycemic control when treatment with both dapagliflozin and metformin is appropriate.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections Special warnings and special precautions for use, Undesirable effects, and Pharmacodynamic properties.

Posology and method of administration

Recommended Dosing

- Healthcare providers should individualize the starting dose of XIGDUO XR based on the patient's current treatment. [See Dosage Forms and Strengths (3).]
- XIGDUO XR should generally be taken orally, once daily with the evening meal
- XIGDUO XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.
- Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin HCl.
- If therapy with a combination tablet containing dapagliflozin and metformin is considered appropriate, the recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin extended-release is 500 mg once daily, which can be titrated to 2000 mg once daily. The maximum dose of XIGDUO XR is dapagliflozin 10 mg/metformin extended-release 2000 mg taken as two 5 mg/1000 mg tablets once daily.

Patients with Renal Impairment

No dosage adjustment for XIGDUO XR is indicated in patients with an eGFR greater than or equal to 45 mL/min/1.73m^2

Assessment of renal function is recommended prior to initiation of XIGDUO XR therapy and periodically thereafter.

XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 m^2.

XIGDUO XR is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m^2 [see *Contraindications*, *Warnings and Precautions*, *Adverse Reactions*, and *Use in Specific Populations*].

Hepatic Impairment

This medicinal product must not be used in patients with hepatic impairment.

Discontinuation for Iodinated Contrast Imaging Procedures

Xigduo XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Xigduo XR if renal function is stable (see Warnings and Precautions).

Contraindications

XIGDUO XR is contraindicated in:

- Patients with severe renal impairment (eGFR below 30 mL/min/1.73 m2), end stage renal disease or patients on dialysis
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin
- Patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients.
- Diabetic pre-coma;
- Acute conditions with the potential to alter renal function such as:
  - Dehydration
  - Severe infection
  - Shock
- Acute or chronic disease which may cause tissue hypoxia such as:
  - Cardiac or respiratory failure
  - Recent myocardial infarction
  - Shock
  - Hepatic impairment
  - Acute alcohol intoxication, alcoholism

XIGDUO XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials because use of such products may result in acute alteration of renal function (see Warnings and Precautions).

Special warnings and special precautions for use

Lactic Acidosis

Metformin hydrochloride

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with XIGDUO XR; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure

who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake when taking metformin since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal, but less than 5 mmol/L, in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions),

prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

Use in Patients with Renal Impairment

Dapagliflozin

The efficacy of dapagliflozin is dependent on renal function. XIGDUO XR is contraindicated in patients with severe renal impairment (CrCl <30 mL/min/1.73m^2). Use of XIGDUO XR is not recommended when the eGFR is less than 45 mL/min/1.73 m2. Therefore, as in all diabetic patients, renal function should be evaluated prior to initiation of XIGDUO XR and periodically thereafter (see section *Posology and Method Of Administration, Contraindications, Special Warnings and Special Precautions for Use and Undesirable Effects*).

Metformin hydrochloride

Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive XIGDUO XR. In the elderly, XIGDUO XR should be carefully titrated to establish the minimum dose for adequate glycemic effect because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, XIGDUO XR should not be titrated to the maximum dose of the metformin component.

Before initiation of XIGDUO XR therapy, and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and XIGDUO XR discontinued if evidence of renal impairment is present.

Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy, or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Use in patients with hepatic impairment

***Metformin* hydrochloride**

Since impaired hepatic function has been associated with some cases of lactic acidosis, XIGDUO XR should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Dapagliflozin

There is limited experience in clinical trials in patients with hepatic impairment.
Dapagliflozin exposure is increased in patients with severe hepatic impairment.
Dapagliflozin should not be used in patients with severe hepatic impairment.

Alcohol intake

Metformin hydrochloride

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Therefore, patients should be warned against excessive alcohol intake, acute or chronic, while receiving XIGDUO XR.

Ketoacidosis

There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking dapagliflozin and other SGLT2 inhibitors,. XIGDUO XR is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with XIGDUO XR who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/l (250 mg/dl). If ketoacidosis is suspected, discontinuation or temporary interruption of XIGDUO XR should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. XIGDUO XR should be used with caution in these patients.

Vitamin B12 levels

Metformin Hydrochloride

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on XIGDUO XR and any apparent abnormalities should be appropriately investigated and managed [see Undesirable effects].

Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. In these patients, routine serum vitamin B12 measurements at 2-to 3-year intervals may be useful.

Surgical Procedures

Metformin hydrochloride

As XIGDUO XR contains metformin hydrochloride, the treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anesthesia. XIGDUO XR should not usually be resumed earlier than 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes
Metformin Hydrochloride
A patient with type 2 diabetes, previously well controlled on XIGDUO XR, who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis or either form occurs, XIGDUO XR must be stopped immediately and other appropriate corrective measures initiated.

Concomitant Medications Affecting Renal Function or Metformin Disposition
Metformin Hydrochloride
Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs [see Drug Interactions] that are eliminated by renal tubular secretion, should be used with caution.

Radiologic Studies with Intravascular Iodinated Contrast Materials
Metformin hydrochloride
Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, XIGDUO XR should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states
Metformin hydrochloride
Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on XIGDUO XR therapy, the drug should be promptly discontinued.

Loss of control of blood glucose
Metformin hydrochloride
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be

necessary to withhold XIGDUO XR and temporarily administer insulin. XIGDUO XR may be reinstituted after the acute episode is resolved.

Use in patients at risk for volume depletion

Dapagliflozin

The diuretic effect of dapagliflozin is a potential concern for volume depleted patients. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted.

When considering initiating dapagliflozin, there may be patients for whom the additional diuretic effect of dapagliflozin is a potential concern either due to acute illness (such as gastrointestinal illness) or a history of hypotension or dehydration with diuretic therapy for patients who may become volume depleted. Initiation of therapy with dapagliflozin is therefore not recommended in these patients.

For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, such as gastrointestinal illness, heat stress or severe infections, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of XIGDUO XR is recommended for patients who develop volume depletion until the depletion is corrected (see section Undesirable Effects).

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension or elderly patients.

Use with Medications Known to Cause Hypoglycemia

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with dapagliflozin (see section Undesirable Effects).

Urosepsis and Pyelonephritis

There have been post marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving XIGDUO XR and other SGLT2 inhibitors. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see section Undesirable Effects).

Pediatric use

Safety and effectiveness of XIGDUO XR in pediatric patients have not been established.

Geriatric use

Because metformin is eliminated by the kidney, and because elderly patients are more likely to have decreased renal function, XIGDUO XR should be used with caution as age increases.

Dapagliflozin

Elderly patients are more likely to have impaired renal function, and/or to be treated with antihypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than younger patients. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment of XIGDUO XR should be based on a careful assessment of renal function.

Lower limb amputations

Dapagliflozin

In one long-term clinical study with another SGLT2 inhibitor, an increase in cases of lower limb amputation (primarily of the toe) has been observed. The medicine in that study is not dapagliflozin. However, it is unknown whether this constitutes a class effect. It is important to regularly examine the feet and counsel all diabetic patients on routine preventative footcare.

Cardiac failure

There is no experience in clinical studies with dapagliflozin in NYHA class IV

Use in patients with diabetes and cardiovascular disease

In two 24-week, placebo-controlled studies with 80-week extension periods, a total of 1887 patients with type 2 diabetes and cardiovascular disease (CVD) were treated with dapagliflozin 10 mg or placebo. Patients with established CVD and inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%), despite pre-existing, stable treatment with oral antidiabetic therapy (OADs) or insulin (alone or in combination) prior to entry, were eligible for these studies and were stratified according to age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (>1 year or <1 year prior to enrollment). Across the 2 studies, 942 patients were treated with dapagliflozin 10 mg and 945 with placebo. Ninety-six percent (96%) of patients treated with dapagliflozin across the 2 studies had hypertension at entry, the majority for more than 10 years duration; the most common qualifying

cardiovascular events were coronary heart disease (75%) and stroke (22%). Approximately 19% of patients received loop diuretics at entry and 15% had congestive heart failure (2% had NYHA Class III). Approximately 37% of patients treated with dapagliflozin 10 mg also received metformin plus one additional OAD at entry, (sulfonylurea, thiazolidinedione, DPP4 inhibitor, or other OAD with or without insulin at entry) 38% received insulin plus at least one OAD, and 18% received insulin alone.

Treatment with dapagliflozin 10 mg as add-on to pre-existing antidiabetic treatments over 24 weeks provided significant improvement in coprimary endpoints of HbA1c and composite clinical benefit compared with placebo in this population. Significant reductions in total body weight and seated systolic blood pressure were also seen (see section Pharmacodynamic Properties). These benefits extended up to 104 weeks of treatment. The safety profile of dapagliflozin in these studies was consistent with that of dapagliflozin in the general clinical study population through 104 weeks of treatment (see section undesirable effects).

In a separate analysis of patients on metformin alone (with or without insulin) in these two studies, similar improvements in HbA1c and percent body weight reduction to those seen in the total study population were seen in patients treated with dapagliflozin 10 mg plus metformin alone compared with placebo plus metformin alone at Week 24. A mean reduction in seated systolic blood pressure was observed, consistent with that seen in the total study population, in patients treated with dapagliflozin 10 mg plus metformin alone compared with placebo plus metformin alone at Week 24 in study 1, but not in study 2.

Interaction with other medicinal products and other forms of interaction
Co-administration of multiple doses of dapagliflozin and metformin did not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects.

There have been no formal interaction studies for XIGDUO XR. The following statements reflect the information available on the individual active substances.

Drug interactions with dapagliflozin
The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In in vitro studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes, and drugs that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. Dapagliflozin is a weak substrate of the P-glycoprotein

(P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effect of Other Drugs on Dapagliflozin

In studies conducted in healthy subjects, the pharmacokinetics of dapagliflozin were not altered by pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate and P-glycoprotein substrate), glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. Following Co-administration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22% decrease and a 51% increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case.

Pioglitazone: Co-administration of a single dose of dapagliflozin (50 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of dapagliflozin with other CYP2C8 substrates would not be expected.

Sitagliptin: Co-administration of a single dose of dapagliflozin (20 mg) and sitagliptin (100 mg), an hOAT-3 substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of dapagliflozin with other hOAT-3 substrates would not be expected.

Glimepiride: Co-administration of a single dose of dapagliflozin (20 mg) and glimepiride (4 mg), a CYP2C9 substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of dapagliflozin with other CYP2C9 substrates would not be expected.

Voglibose (α-glucosidase inhibitor): Co-administration of a single dose of dapagliflozin (10 mg) and voglibose (0.2 mg three times per day) did not alter the pharmacokinetics of dapagliflozin.

Hydrochlorothiazide: Co-administration of a single dose of dapagliflozin (50 mg) and hydrochlorothiazide (25 mg) did not alter the pharmacokinetics of dapagliflozin.

Bumetanide: Co-administration of multiple once-daily doses of dapagliflozin (10 mg) and multiple once-daily doses of bumetanide (1 mg) did not alter the pharmacokinetics of dapagliflozin. Co-administration of dapagliflozin and bumetanide did not meaningfully change

the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

Valsartan: Co-administration of a single dose of dapagliflozin (20 mg) and valsartan (320 mg) did not alter the pharmacokinetics of dapagliflozin.

Simvastatin: Co-administration of a single dose of dapagliflozin (20 mg) and simvastatin (40 mg), a CYP3A4 substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of dapagliflozin with other CYP3A4 substrates would not be expected.

Rifampin: Co-administration of a single dose of dapagliflozin (10 mg) and rifampin (rifampicin), an inducer of various active transporters and drug-metabolizing enzymes, dosed to steady-state (600 mg/day) resulted in a decrease in dapagliflozin Cmax and AUC by 7% and 22%, respectively. The mean amount of glucose excreted in the urine over 24 hours following administration of dapagliflozin alone (51 g) was not markedly affected by rifampin Co-administration (45 g). No dose adjustment of dapagliflozin is recommended when dapagliflozin is co-administered with rifampin.

Mefenamic Acid: Co-administration of a single dose of dapagliflozin (10 mg) and mefenamic acid, an inhibitor of UGT1A9, dosed to steady-state (250 mg every 6 hours) resulted in an increase in dapagliflozin Cmax and AUC by 13% and 51%, respectively. The mean amount of glucose excreted in the urine over 24 hours following administration of dapagliflozin alone was not markedly affected by mefenamic acid Co-administration. No dose adjustment of dapagliflozin is recommended when dapagliflozin is co-administered with mefenamic acid.

Effect of Dapagliflozin on Other Drugs

In studies conducted in healthy subjects, as described below, dapagliflozin did not alter the pharmacokinetics of pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin, or warfarin.

Pioglitazone: Co-administration of a single dose of dapagliflozin (50 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of pioglitazone. Therefore, dapagliflozin does not meaningfully inhibit CYP2C8-mediated metabolism.

Sitagliptin: Co-administration of a single dose of dapagliflozin (20 mg) and sitagliptin (100 mg), an hOAT-3 substrate, did not alter the pharmacokinetics of sitagliptin. Therefore, dapagliflozin is not an inhibitor of hOAT-3 transport pathway.

Glimepiride: Co-administration of a single dose of dapagliflozin (20 mg) and glimepiride (4 mg), a CYP2C9 substrate, did not alter the pharmacokinetics of glimepiride. Therefore, dapagliflozin is not an inhibitor of CYP2C9-mediated metabolism.

Hydrochlorothiazide: Co-administration of a single dose of dapagliflozin (50 mg) and hydrochlorothiazide (25 mg) did not alter the pharmacokinetics of hydrochlorothiazide.

Bumetanide: Co-administration of a multiple once-daily doses of dapagliflozin (10 mg) and multiple once-daily doses of bumetanide (1 mg) increased both Cmax and AUC bumetanide values by 13%. Co-administration of dapagliflozin did not meaningfully alter the steady-state pharmacodynamics responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Valsartan: Co-administration of a single dose of dapagliflozin (20 mg) and valsartan (320 mg) did not alter the pharmacokinetics of valsartan.

Simvastatin: Co-administration of a single dose of dapagliflozin (20 mg) and simvastatin (40 mg), a CYP3A4 substrate, did not affect the Cmax of simvastatin but increased the AUC by 20%, which was not considered to be clinically relevant. Therefore, dapagliflozin does not meaningfully inhibit CYP3A4-mediated metabolism.

Digoxin: Co-administration of dapagliflozin (10 mg once daily following a 20-mg loading dose) and a single dose of digoxin (0.25 mg), a P-glycoprotein substrate, did not affect the pharmacokinetics of digoxin. Therefore, dapagliflozin does not meaningfully inhibit or induce P-gp-mediated transport.

Warfarin: Co-administration of dapagliflozin (10 mg once daily following a 20-mg loading dose) and a single dose of warfarin (25 mg) did not affect the pharmacokinetics of S-warfarin, a CYP2C19 substrate. Therefore, dapagliflozin does not meaningfully inhibit or induce CYP2C19-mediated metabolism. Dapagliflozin also did not affect the pharmacokinetics of R-warfarin. Additionally, dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio [INR]).

Lithium: Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

Drug interactions with metformin
Cationic Drugs
Metformin hydrochloride

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Glyburide

Metformin hydrochloride

In a single-dose interaction study in type 2 diabetes patients, Co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and maximum concentration (Cmax) were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide

Metformin hydrochloride

A single-dose, metformin-furosemide drug-interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by Co-administration. Furosemide increased the metformin plasma and blood Cmax by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine

Metformin hydrochloride

A single-dose, metformin-nifedipine drug-interaction study in normal healthy volunteers demonstrated that Co-administration of nifedipine increased plasma metformin Cmax and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. Tmax and

half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Use with Other Drugs

Metformin hydrochloride

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin, the patient should be closely observed for loss of blood glucose control.

When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and, therefore, is less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Other interactions

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of dapagliflozin have not been specifically studied.

Interference with 1.5-anhydroglucitol (1.5.AG) Assay

Monitoring glycemic control with 1.5-AG assay is not recommended as measurements of 1.5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Pregnancy and lactation

Pregnancy

XIGDUO XR must not be used in the second and third trimesters of pregnancy. In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny (see section Preclinical safety data).

In conventional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of non-renal organogenesis

in humans. No developmental toxicities were observed in rabbits at any dose tested (1191× the maximum recommended human dose [MRHD]). In rats, dapagliflozin was neither embryolethal nor teratogenic (1441× the MRHD) in the absence of maternal toxicity.

Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

There are no adequate and well-controlled studies of XIGDUO XR in pregnant women. When pregnancy is detected, XIGDUO XR should be discontinued.

Lactation
XIGDUO XR must not be used by a nursing woman.

No studies in lactating animals have been conducted with the combined components of XIGDUO XR. In studies performed with the individual components, both dapagliflozin and metformin are excreted in the milk of lactating rats.

Direct and indirect exposure of dapagliflozin to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight gain associated with lactational exposure in weanling juvenile rats suggest that dapagliflozin must be avoided during the first 2 years of life (see section Preclinical safety data).

It is not known whether dapagliflozin or metformin are secreted in human milk.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.
It should be taken into account that dizziness has been reported in studies with dapagliflozin

Undesirable effects
Clinical experience
Dapagliflozin and metformin hydrochloride
Data from a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin co-administered with metformin immediate- or extended-release was used to evaluate safety data. This pool included several add-on studies (metformin alone and in combination with a DPP4 inhibitor and metformin, or insulin and metformin, 2 initial

combination with metformin studies, and 2 studies of patients with cardiovascular disease (CVD) and type 2 diabetes who received their usual treatment (with metformin as background therapy). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

The overall incidence of adverse events for the 8-study, short-term, placebo-controlled pool in patients treated with dapagliflozin 10 mg and metformin was 60.3% compared to 58.2% for the placebo and metformin group. Discontinuation of therapy due to adverse events in patients who received dapagliflozin 10 mg and metformin was 4% compared to 3.3% for the placebo and metformin group. The most commonly reported events leading to discontinuation and reported in at least 3 patients treated with dapagliflozin 10 mg and metformin were renal impairment (0.7%), increased blood creatinine (0.2%), decreased renal creatinine clearance (0.2%), and urinary tract infection (0.2%).

The adverse reactions in the 8-study, short-term, placebo-controlled pooled analysis reported (regardless of investigator assessment of causality) in ≥2% of patients treated with dapagliflozin 10 mg and metformin, and ≥1% more frequently than patients treated with placebo and metformin, are shown in Table 1.

Table 1: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies* Reported in ≥2% of Patients Treated with Dapagliflozin 10 mg and Metformin, and ≥1% More Frequently than in Patients Treated with Placebo and Metformin (Excluding Hypoglycemia)†

System and Organ Class Preferred Term	Dapagliflozin 10 mg and metformin N=983
Infections and Infestations Genital infection‡	Common
Infections and Infestations Urinary tract infection§	Common
Renal Urinary Disorders Polyuria¶	Common

* The 8 placebo-controlled studies included 2 initial combination with metformin, 2 add-on to metformin, 1 add-on to insulin, 1 add-on to sitagliptin, and 2 studies with combination add-on therapy. Table shows up to 24-week (short-term) data regardless of glycemic rescue.
† For hypoglycemia information see Hypoglycemia subsection.
‡ Genital infection includes the following preferred terms, listed in order of frequency reported: vulvovaginal mycotic infection, balanitis, vaginal infection, genital infection fungal, genital infection, vulvovaginal candidiasis, balanitis candida, vulvovaginitis, genital candidiasis, vulvitis, balanoposthitis, genital infection male, genitourinary tract infection, penile abscess, penile infection, posthitis, vulval abscess, and vaginitis bacterial.
§ Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis,
trigonitis, urethritis, kidney infection, and prostatitis.
¶ Polyuria includes the preferred terms, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased

Dapagliflozin
Two major pools of patients were used to evaluate adverse reactions with dapagliflozin 10 mg versus control, a placebo-controlled study pool and a larger pool of active and placebo controlled studies.

Placebo-Controlled Studies
The first pool is a prespecified pool of patients from 13 short-term, placebo-controlled studies used to evaluate and present all safety data for dapagliflozin other than malignancies, liver tests, and hypoglycemia (evaluated by individual study). This pool included the monotherapy studies, several add-on studies (metformin, sulfonylurea, pioglitazone, DPP4 inhibitor, insulin, and two studies with a combination of add-on therapies), and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with dapagliflozin 10 mg and 2295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies).

These 13 studies provide a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population was male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, mean HbA1c was 8.2%, and renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients.

Active- and Placebo-Controlled Studies

The second pool is a pool of patients from 21 active- and placebo-controlled studies used to evaluate and present data for malignancies and liver tests. In this pool, 5936 patients were treated with dapagliflozin and 3403 were treated with control (either as monotherapy or in combination with other antidiabetic therapies).

These 21 studies provide a mean duration of exposure to dapagliflozin 10 mg of 55 weeks (6247 patient-years). Across both treatment groups, the mean age of the population was 58 years and 3.5% were older than 75 years. Fifty-six percent (56%) of the population was male;77% were White, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 7 years, 34% of patients had a history of cardiovascular disease, mean HbA1c was 8.2%, and baseline renal function was normal or mildly impaired in 89% of patients and moderately impaired in 11% of patients.

Additionally, dapagliflozin 5 mg was evaluated in a 12-study, short-term, placebo-controlled pool of patients that included 1145 patients treated with dapagliflozin 5 mg as monotherapy or in combination with other antidiabetic therapy (mean exposure = 22 weeks) and 1393 patients treated with placebo as monotherapy or in combination with other antidiabetic therapy (mean exposure = 21 weeks). All safety data presented for dapagliflozin 5 mg is from this pool.

The overall incidence of adverse events for the 13-study, short-term, placebo-controlled pool (short-term treatment) in patients treated with dapagliflozin 10 mg was 60.0% compared to 55.7% for the placebo group. Discontinuation of therapy due to adverse events in patients who received dapagliflozin 10 mg was 4.3% compared to 3.6% for the placebo group. The most commonly reported events leading to discontinuation and reported in at least 3 dapagliflozin 10 mg-treated patients were renal impairment (0.8%), decrease in creatinine clearance (0.6%), increased blood creatinine (0.3%), urinary tract infections (0.2%), and vulvovaginal mycotic infection (0.1%).

The adverse reactions in this 13-study placebo-controlled pooled analysis reported (regardless of investigator assessment of causality) in ≥2% of patients treated with dapagliflozin 10 mg, and ≥1% more frequently than patients treated with placebo, are shown in Table 2.

Table 2: Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with XIGDUO 10 mg and ≥1% More Frequently than in Patients Treated with Placebo (Excluding Hypoglycemia)[*,†]

System Organ Class Preferred Term	XIGDUO 10 mg N=2360
Infections and Infestations	Common

Genital infection‡	
Infections and Infestations Urinary tract infection§	Common
Musculoskeletal and Connective Tissue Disorders Back pain	Common
Renal Urinary Disorders Polyuria¶	Common

* The 13 placebo-controlled studies included 3 monotherapy, 1 initial combination with metformin, 2 add-on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone, 1 add-on to sitagliptin, 1 add-on to glimepiride, and 2 studies with combination add-on therapy. Table shows up to 24-week (short-term) data regardless of glycemic rescue.

† For hypoglycemia information see Hypoglycemia subsection.

‡ Genital infection includes the following preferred terms, listed in order of frequency reported: vulvovaginal mycotic infection, balanitis, vaginal infection, genital infection fungal, genital infection, vulvovaginal candidiasis, balanitis candida, vulvovaginitis, genital candidiasis, vulvitis, balanoposthitis, genital infection male, genitourinary tract infection, penile abscess, penile infection, posthitis, vulval abscess, and vaginitis bacterial.

§ Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

¶ Polyuria includes the preferred terms, listed in order of frequency reported: pollakiuria, polyuria, urine output increased.

Additional adverse reactions in ≥5% of patients treated with dapagliflozin 10 mg, ≥1% more than patients in placebo/comparator, and reported in at least three more patients treated with dapagliflozin 10 mg and regardless of relationship to dapagliflozin reported by investigator, were reviewed by treatment regimen. The only study with a metformin treatment component meeting these criteria was: add-on to metformin: headache (5.3% dapagliflozin 10 mg and 3.1% placebo).

In a dedicated of patients with moderate renal impairment, 13 patients with an adverse event of bone fracture were reported up to Week 104, of which 8 occurred in the dapagliflozin 10 mg group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73 m2 and 10 of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the site of fracture. At Week 52 and persisting through Week 104, greater increases in mean parathyroid hormone (PTH) and serum phosphorus were observed in this study for patients treated with dapagliflozin 10 mg compared with placebo, where baseline values of these analytes were higher.

Cardiovascular Outcomes Study (DECLARE)

In the DECLARE study, [see Clinical Trials], 8574 patients received dapagliflozin 10 mg and 8569 received placebo for a median exposure time of 48 months. In total, there were 30623 patient years of exposure to dapagliflozin.

Volume depletion

Adverse reactions for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3:

Table 3: Adverse Reactions Related to Volume Depletion* in Clinical Studies with Dapagliflozin

	Pool of 12 Placebo-Controlled Studies			**Pool of 13 Placebo-Controlled Studies**		**DECLARE Study**	
	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=551 (1.8%)	n=400	n=313 (9.7%)	n=2674 (1.5%)	n=2366 (2.5%)	n=93457 (6.1%)[i]	n=86657 (6.6%)[ii]
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m^2	n=1072 (1.9%)	n=1071 (0.9%)	n=891 (1.1%)	n=2684 (1.5%)	n=2655 (1.9%)	N=65830 (4.6%)	n=60435 (5.8%)
Patients ≥65 years of age	n=2761 (0.4%)	n=2161 (0.5%)	n=2043 (1.5%)	n=7116 (0.8%)	n=66511 (1.7%)	n=3950121 (3.1%)	n=3948117 (3.0%)

Events suggestive of volume depletion (including reports of dehydration, hypovolemia, or hypotension) were reported in 1.1% and 0.7% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. Serious events occurred in ≤0.2% of patients across 21 active- and placebo-controlled studies (dapagliflozin as monotherapy or in combination with other antidiabetic therapies) and were balanced between dapagliflozin 10 mg and comparator.

Genital Infections

Events of genital infections were reported in 5.5% and 0.6% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. The events of genital infections reported in patients treated with dapagliflozin 10 mg were all mild to moderate. Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0.2% dapagliflozin 10 mg vs.. 0% in placebo). Infections were reported more frequently in females (8.4% dapagliflozin 10 mg vs. 1.2% placebo) than in males (3.4% dapagliflozin 10 mg vs. 0.2% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

In the DECLARE study, the number of patients with serious adverse events of genital mycotic infections were few and balanced: 2 (<0.1%) patients in each of the dapagliflozin-treated and placebo groups.

Urinary tract infections
In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin compared with placebo (4.7% versus 3.5%, respectively; see section Special Warning and Precautions). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

In the dapagliflozin cardiovascular outcomes study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

Hypoglycemia
In studies with dapagliflozin in add-on combination with metformin, minor episodes of hypoglycemia were reported at similar frequencies in the group treated with dapagliflozin 10 mg plus metformin (6.9%) and in the placebo plus metformin group (5.5%). No major events of hypoglycemia were reported.
In an add-on to metformin study up to 24 weeks, minor episodes of hypoglycemia were reported in 12,8% of subjects who received dapagliflozin 10 mg plus metformin and in 3,7% of subjects who received placebo plus metformin. No major events of hypoglycemia were reported.

Table 4: Incidence of Major* and Minor† Hypoglycemia in Placebo-Controlled Study

DECLARE Study (48 months median exposure)[iii]			
All Patients[iv]	**Placebo N=8569**		**Dapagliflozin 10 mg N=8574**
Major [n (%)]	83 (1.0)	–	58 (0.7)
Patients treated with Insulin[v]	**N=4606**	–	**N=4177**
Major [n (%)]	64 (1.4)	–	52 (1.2)
Patients treated with a Sulfonylurea[vi]	**N=4521**	–	**N=4118**
Major [n (%)]	23 (0.5)	–	14 (0.3)

* Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.

Events Related to Decreased Renal Function

In the 13-study, short-term, placebo-controlled pool, reported terms referring to events related to decreased renal function were grouped (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate). This group of events was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥60 mL/min/1.73m2) events related to decreased renal function were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively.

Events related to decreased renal function were more common in patients with baseline eGFR ≥30 and <60 mL/min/1.73m2 (18.5% dapagliflozin 10 mg vs. 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤44 µmol/L from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment

Data from the DECLARE study showed that long-term exposure (up to 60 months) to dapagliflozin 10 mg, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m2), was not associated with an increased risk for renal-related adverse events. There were fewer patients with marked laboratory abnormalities of creatinine, creatinine clearance, eGFR, and urine albumin to creatinine ratio (UACR) in the dapagliflozin 10 mg treated group compared with the placebo group. eGFR decreased over time in both treatment groups (see Table 5).

Table 5: Changes in Serum Creatinine and eGFR Associated with dapagliflozin in the DECLARE study

		DECLARE Study			
		Placebo		FORXIGA 10 mg	
			N		N
Baseline Mean	Serum Creatinine (mg/dL)	0.864	8569	0.863	8573
	eGFR (mL/min/1.73 m^2)	85.1	8569	85.4	8573
6 Months Change	Serum Creatinine (mg/dL)	0.010	8081	0.035	8117
	eGFR (mL/min/1.73 m^2)	-1.0	8080	-2.9	8114
1 Year Change	Serum Creatinine (mg/dL)	0.018	7673	0.036	7754
	eGFR (mL/min/1.73 m^2)	-1.8	7672	-3.2	7754
2 Year Change	Serum Creatinine (mg/dL)	0.045	7020	0.045	7211
	eGFR (mL/min/1.73 m^2)	-4.1	7009	-4.1	7200
3 Year Change	Serum Creatinine (mg/dL)	0.074	6372	0.058	6722
	eGFR (mL/min/1.73 m^2)	-6.6	6367	-5.8	6718
4 Year Change	Serum Creatinine (mg/dL)	0.106	5287	0.082	5613
	eGFR (mL/min/1.73 m^2)	-9.4	5285	-8.1	5612

Ketoacidosis
In the DECLARE study with a median exposure time of 48 months, events of diabetic ketoacidosis (DKA) were reported in 27 patients in the dapagliflozin-treated group and 12 patients in the placebo group. The events were evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin-treated group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population *(*Special warnings and special precautions for use).

Monotherapy - metformin hydrochloride
The most common adverse reactions in placebo-controlled clinical trials reported in >5% of patients treated with metformin hydrochloride extended-release and more commonly than in placebo-treated patients included diarrhea and nausea/vomiting (both very common).

Laboratory findings
Hematocrit
Dapagliflozin
In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in dapagliflozin-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were 2.30% in the dapagliflozin 10 mg group versus −0.33% in the placebo group. At Week 102, the mean changes were 2.68% versus −0.46%,

respectively. By Week 24, hematocrit values >55% were reported in 1.3% of dapagliflozin 10-mg–treated patients versus 0.4% of placebo-treated patients. Results were similar during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year).

Serum Inorganic Phosphorus

Dapagliflozin

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10-mg-treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL vs. −0.04 mg/dL, respectively). Similar results were seen at Week 102. Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in dapagliflozin 10 mg group versus placebo at Week 24 (1.7% vs. 0.9%, respectively) and during the short-term plus long-term phase (3.0% vs. 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

Dapagliflozin

In the pool of 13 placebo-controlled studies, small changes from baseline in mean lipid values were reported at Week 24 in dapagliflozin-10-mg−treated patients compared with placebo treated patients. Mean percent change from baseline at Week 24 for dapagliflozin 10 mg versus placebo, respectively, was as follows: total cholesterol, 2.5% versus 0.0%; HDL cholesterol, 6.0% versus 2.7%; LDL cholesterol, 2.9% versus −1.0%; triglycerides, −2.7% versus −0.7%. Mean percent change from baseline at Week 102 for dapagliflozin 10 mg versus placebo, respectively, was as follows: total cholesterol, 2.1% versus −1.5%; HDL cholesterol, 6.6% versus 2.1%; LDL cholesterol, 2.9% versus −2.2%; triglycerides, −1.8% versus −1.8%. The ratio between LDL cholesterol and HDL cholesterol decreased for both treatment groups at Week 24. In the DECLARE study, mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in dapagliflozin 10 mg-treated and the placebo groups, respectively.

Vitamin B12 Levels

Metformin hydrochloride

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation (see section Special warning and special precaution for use).

Postmarketing Experience

Dapagliflozin

Additional adverse reactions have been identified during postapproval use of dapagliflozin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury and Impairment in Renal Function
- Urosepsis and Pyelonephritis
- Rash

Metformin

Cholestatic, hepatocellular, and mixed hepatocellular liver injury.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Pusat Farmakovigilans: Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekursor, dan Zat Adiktif Badan Pengawas Obat dan Makanan Republik Indonesia

Address: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

Phone: +62-21- 4244691 Ext. 1079

Website: http://e-meso.pom.go.id/

Overdosage

Dapagliflozin

Orally administered dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the MRHD). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycemia for patients treated with dapagliflozin was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) of dapagliflozin were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycemia for subjects administered

dapagliflozin was slightly higher than placebo and was not dose related. Rates of adverse events including dehydration or hypotension for patients treated with dapagliflozin were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

Metformin-hydrochloride
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is hemodialysis. Events of hypoglycemia have been reported with overdoses of metformin, although a causal association has not been established.

Pharmacological Properties

Mechanism of Action

XIGDUO XR

XIGDUO XR combines two antihyperglycemic agents with complementary mechanisms of action to improve both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with type 2 diabetes: dapagliflozin, an SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium glucose cotransporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis). Dapagliflozin is orally available and requires once-daily dosing.

SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder, and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycemia in type 2 diabetes mellitus, reabsorption of filtered glucose continues. Dapagliflozin reduces maximum tubular glucose transport by 55% and reduces renal glucose reabsorption such that glucose appears in the urine

at normal plasma glucose levels. Thus, dapagliflozin improves both fasting and postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24- hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in healthy subjects with normal glucose, dapagliflozin has a low propensity to cause hypoglycemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta-cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of weight reduction is body-fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy x-ray absorptiometry (DXA) and magnetic resonance imaging. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is greater than 1400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Metformin hydrochloride

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see section Special warning and special precautions for use) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Pharmacodynamic properties

General

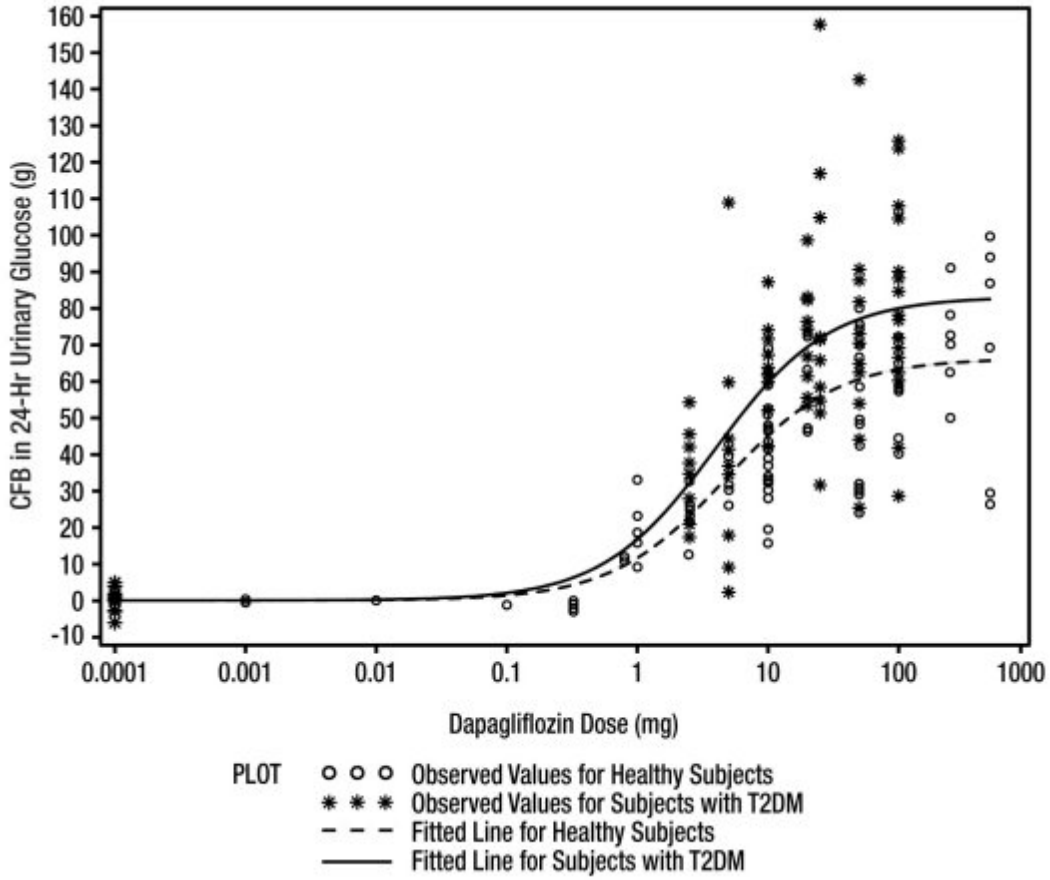
Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (Figure 1). Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 0.33 mg/dL to 0.87 mg/dL.

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)



Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) dapagliflozin in healthy subjects.

Clinical Trial Information

The Co-administration of dapagliflozin and metformin IR or XR has been studied in patients with type 2 diabetes inadequately controlled on metformin. Treatment with dapagliflozin plus metformin at all doses, produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c, and fasting plasma glucose (FPG) compared to control.

In a dedicated clinical study, decrease in weight was mainly attributable to a reduction in body-fat mass as measured by DXA. Dapagliflozin twice-daily treatment added to metformin was shown to be effective and safe in type 2 diabetic patients.

Additionally, dapagliflozin 10 mg or placebo were studied in type 2 diabetes patients with cardiovascular disease (approximately 37% of patients across 2 studies received dapagliflozin 10 mg or placebo plus metformin alone and type 2 diabetes patients with hypertension (approximately 90% of patients across 2 studies received dapagliflozin 10 mg or placebo plus metformin). In two studies of dapagliflozin 10 mg in type 2 diabetes patients with cardiovascular disease, statistically significant improvements in HbA1c and significant reductions in body weight and seated systolic blood pressure were seen at Week 24 in patients treated with dapagliflozin 10 mg compared to those treated with placebo, and were sustained through Week 104. In two studies of dapagliflozin 10 mg in type 2 diabetes patients with hypertension, statistically significant reductions in mean seated systolic blood pressure were also seen in patients treated with dapagliflozin 10 mg combined with other OADs and antihypertensive treatments (an ACE or ARB in one study and an ACE or ARB plus one additional antihypertensive treatment in another study) compared to those treated with placebo at Week 12.

There have been no clinical efficacy studies conducted with XIGDUO XR/XIGDUO IR; however, XIGDUO XR/XIGDUO IR is considered to be equivalent to co-administered dapagliflozin and metformin hydrochloride extended-release and immediate-release tablets (see section Pharmacokinetics properties).

Combination Therapy with Metformin

A total of 1236 patients with inadequately controlled type 2 diabetes (HbA1c greater than or equal to 7.5% and less than or equal to 12%) participated in two active-controlled studies of 24-weeks duration to evaluate the efficacy and safety of dapagliflozin 5 mg or 10 mg in combination with metformin extended-release formulation (XR).

641 patients were randomised to one of three treatment arms following a 1-week lead-in period: dapagliflozin 10 mg plus metformin XR (up to 2000 mg per day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin dose was up-titrated weekly in 500 mg increments, as tolerated, with the maximum and median dose achieved being 2000 mg.

The combination treatment of dapagliflozin 10 mg plus metformin provided significant improvements in haemoglobin A1c (HbA1c) and FPG, compared with either of the monotherapy treatments and significant improvements in body weight compared with metformin alone (Table 6, Figures 2 and 3). Dapagliflozin 10 mg as monotherapy also provided significant improvements in FPG and body weight compared with metformin alone and was non-inferior to metformin monotherapy in lowering HbA1c. The proportion of patients who were rescued or discontinued for lack of glycaemic control during the 24 week double- blind treatment period (adjusted for baseline HbA1c) was higher on treatment with metformin plus placebo (13.5%) than on dapagliflozin 10 mg plus placebo and dapagliflozin 10 mg plus metformin (7.8%, and 1.4%).

Table 6. Results at Week 24 (LOCF*) in an Active-Controlled Study of Dapagliflozin Combination Therapy with Metformin XR

Efficacy Parameter	**Dapagliflozin 10 mg + Metformin XR**	**Dapagliflozin 10 mg**	**Metformin XR**
	N=211†	**N=219†**	**N=208†**
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline (adjusted mean‡)	−1.98	−1.45	−1.44
Difference from dapagliflozin (adjusted mean‡) (95% CI)	−0.53§ (−0.74, −0.32)		
Difference from metformin (adjusted mean‡) (95% CI)	−0.54§ (−0.75, −0.33)	−0.01¶ (−0.22, 0.20)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%#	31.7%	35.2%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−2.59#	−2.14	−2.05
FPG (mg/dL)			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean‡)	−60.4	−46.4	−34.8
Difference from dapagliflozin (adjusted mean‡) (95% CI)	−13.9§ (−20.9, −7.0)		
Difference from metformin (adjusted mean‡) (95% CI)	−25.5§ (−32.6, −18.5)	−11.6¶ (−18.6, −4.6)	
Body Weight (kg)			
Baseline (mean)	88.56	88.53	87.24
Change from baseline (adjusted mean‡)	−3.33	−2.73	−1.36

Difference from metformin (adjusted mean‡) (95% CI)	−1.97§ (−2.64, −1.30)	−1.37§ (−2.03, −0.71)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

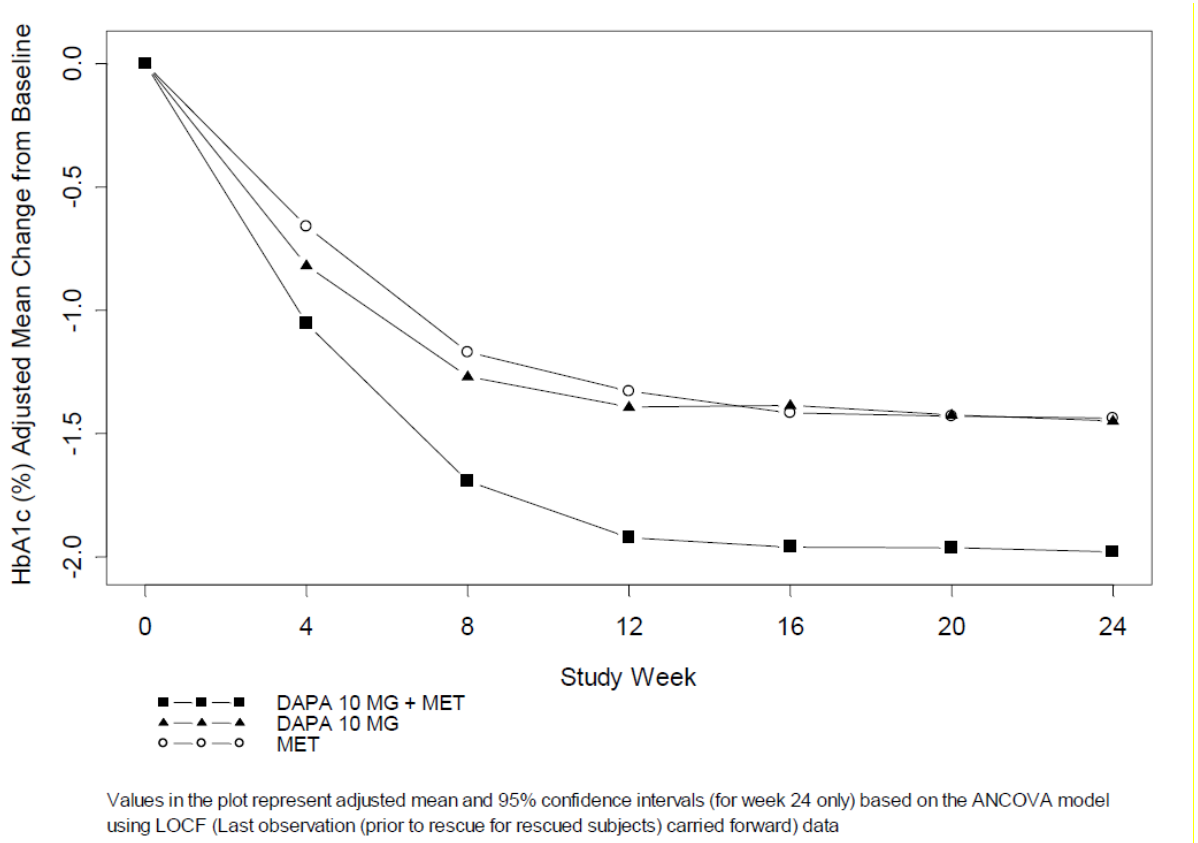
‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ Non-inferior *versus* metformin.

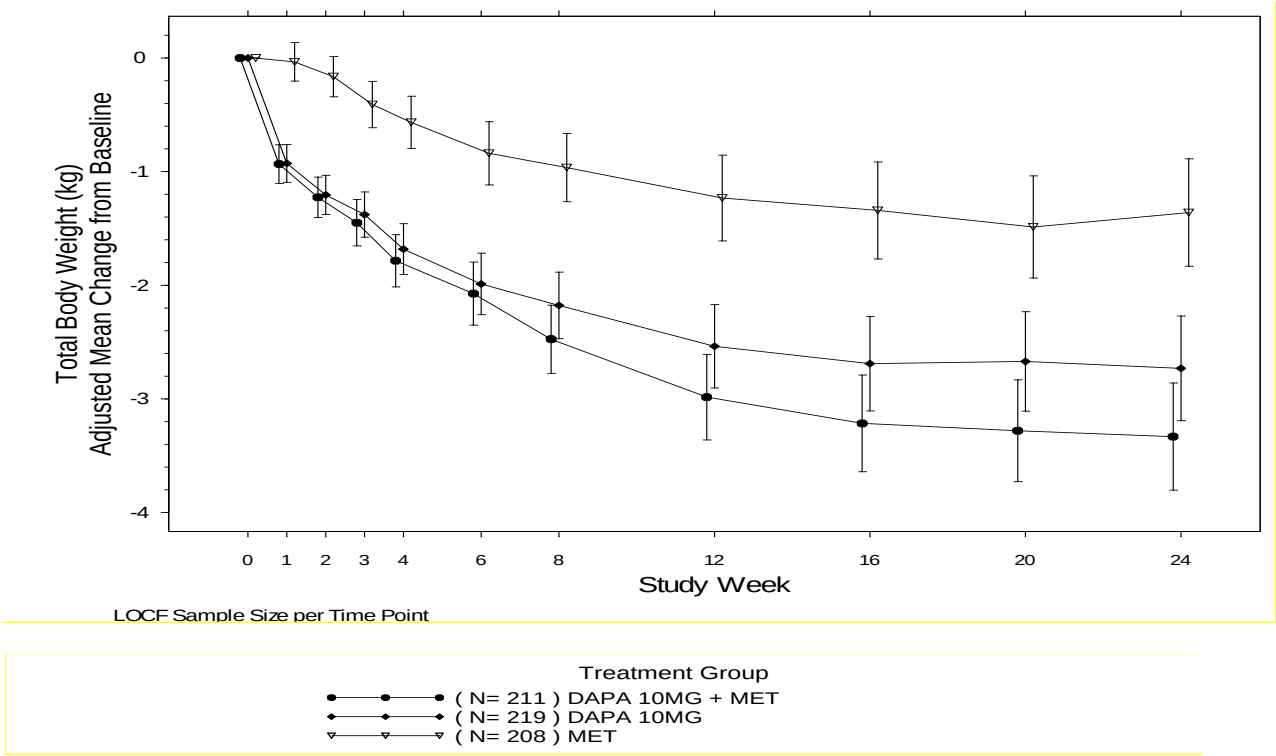
p-value <0.05.

Figure 2: Adjusted Mean Change from Baseline Over Time (LOCF[a]) in HbA1c (%) in a 24 Week Active-Controlled Study of Dapagliflozin Combination Therapy with Metformin XR



Values in the plot represent adjusted mean and 95% confidence intervals (for week 24 only) based on the ANCOVA model using LOCF (Last observation (prior to rescue for rescued subjects) carried forward) data

Figure 3: Adjusted Mean Change from Baseline Over Time (LOCF[a]) in Total Body Weight (kg) in a 24-Week Active-Controlled Study of Dapagliflozin Combination Therapy with Metformin XR



[a] LOCF: last observation (prior to rescue for rescued patients) carried forward
Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Another 24-week study evaluating dapagliflozin 5 mg plus metformin XR showed clinically relevant and statistically significant improvements in glycemic parameters *versus* dapagliflozin 5 mg monotherapy and metformin XR monotherapy.

Addition of dapagliflozin to metformin IR

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study with a 78-week controlled, blinded extension period to evaluate dapagliflozin in combination with metformin. Patients on metformin at a dose of at least 1500 mg/day were randomized after completing a 2-week, single-blind, placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 2.5 mg, 5 mg or 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, dapagliflozin 10 mg provided significant improvements in HbA1c, and FPG, and significant reduction in body weight compared with placebo at week 24 (Table 7). At Week 102, adjusted mean change from baseline in HbA1c (Figure 4), FPG, and body weight was −0.78%, −24.5 mg/dL, and −2.81 kg, respectively, for patients treated with

dapagliflozin 10 mg plus metformin and 0.02%, −10.4 mg/dL, and −0.67 kg for patients treated with placebo plus metformin based on the longitudinal repeated measures analysis excluding data after rescue. The proportion of patients who were rescued or discontinued for lack of glycemic control during the 24-week double-blind treatment period (adjusted for baseline HbA1c) was higher in the placebo plus metformin group (15.0%) than in the dapagliflozin 10 mg plus metformin group (4.4%). By week 102 (adjusted for baseline HbA1c), more patients treated with placebo plus metformin (60.1%) required rescue therapy than patients treated with dapagliflozin 10 mg plus metformin (44.0%).

Table 7: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

Efficacy Parameter	**Dapagliflozin 10 mg + Metformin N=135†**	**Placebo + Metformin N=137†**
HbA1c		
Baseline (mean)	7.92	8.11
Change from baseline (adjusted mean‡)	−0.84	−0.30
Difference from dapagliflozin (adjusted mean‡) (95% CI)	−0.54§ (−0.74, −0.34)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%¶	25.9%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−1.32¶ (N= 18)	−0.53 (N= 22)
FPG (mg/dL)		
Baseline (mean)	156.0	165.6
Change from baseline at Week 24 (adjusted mean‡)	−23.5	−6.0
Difference from placebo (adjusted mean‡) (95% CI)	−17.5§ (−25.0, −10.0)	
Change from baseline at Week 1 (adjusted mean‡)	−16.5§ (N=115)	1.2 (N=126)
Body Weight (kg)		

Baseline (mean)	86.28	87.74
Change from baseline (adjusted mean‡)	−2.86	−0.89
Difference from metformin XR (adjusted mean‡) (95% CI)	−1.97§ (−2.63,−1.31)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

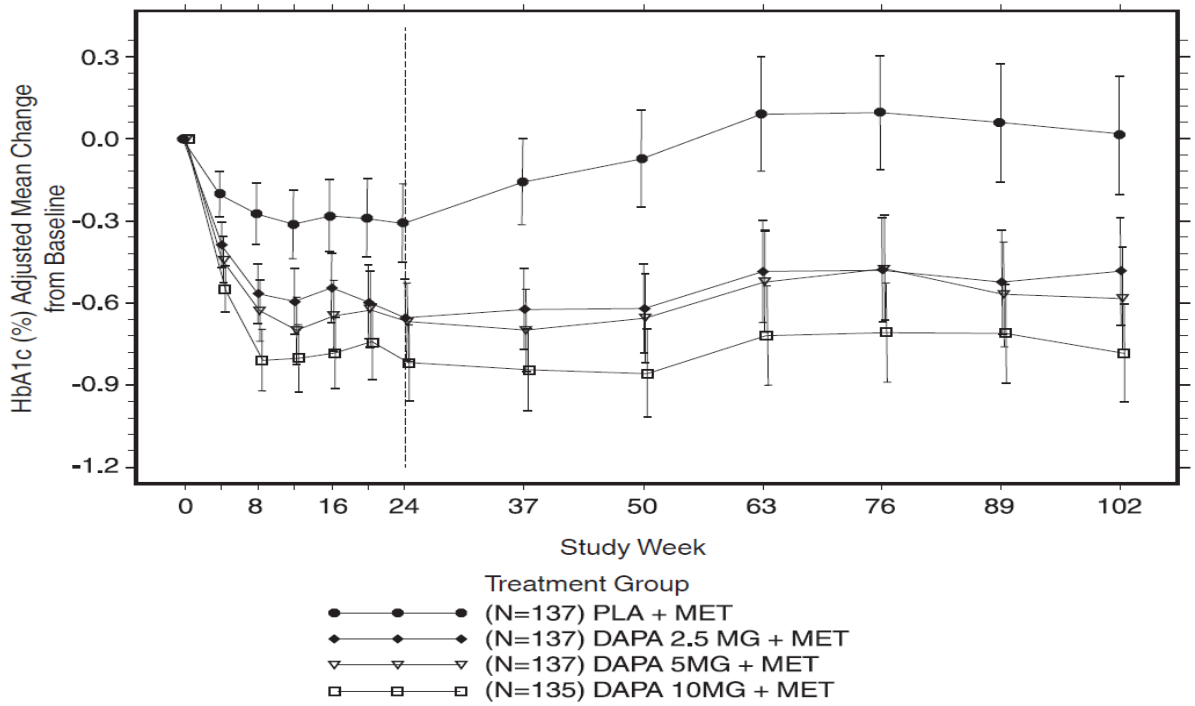
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.00001 versus placebo + metformin.

¶ p-value <0.05 versus placebo + metformin

Figure 4: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 102-Week Placebo-Controlled Study of Dapagliflozin in Combination with Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)



Dapagliflozin twice-daily add-on to metformin IR

A total of 399 patients with type 2 diabetes and inadequate glycemic control on metformin alone were randomized in this 16-week, placebo-controlled study to evaluate dapagliflozin 2.5 mg twice daily and 5 mg twice daily as add-on therapy to metformin. Recruitment was stratified by HbA1c <7.0% (approximately 15% of patients) and HbA1c ≥7.0% (approximately 85% of

patients) at randomization. Patients on metformin at a dose of at least 1500 mg per day were randomized following a 4-week single-blind, placebo lead-in period to dapagliflozin 5 mg, dapagliflozin 2.5 mg or placebo twice daily. An additional double-blind arm of the study included patients received 10 mg dapagliflozin once daily co-administered with metformin as a 'positive control,' a measure of assay sensitivity. Efficacy and safety in this dapagliflozin once-daily treatment arm was compared only to placebo co-administered with metformin.

As add-on treatment to metformin, dapagliflozin 5 mg twice daily provided significant improvements in HbA1c and FPG, and significant reduction in body weight compared with placebo twice daily at Week 16 and was consistent with glycemic and body-weight changes seen with dapagliflozin 10 mg once-daily treatment (see Table 8). Dapagliflozin 2.5 mg plus metformin twice-daily treatment also significantly improved HbA1c (−0.52%) compared to placebo plus metformin twice-daily treatment (−0.30%) at Week 16 ($p< 0.05$).

Table 8: Results of a 16-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin Twice Daily in Add-On Combination with Metformin

Efficacy Parameter	**Dapagliflozin 5mg BID + Metformin N=99†**	**Placebo BID + Metformin N=101†**
HbA1c		
Baseline (mean)	7.79	7.94
Change from baseline (adjusted mean‡)	−0.65	−0.30
Difference from Placebo (adjusted mean‡) (95% CI)	−0.35§ (−0.52, −0.18)	
Percent of patients with HbA1c >7.0% at baseline achieving HbA1c <7% adjusted for baseline at Week 16	38.2¶ (N=90)	21.4 (N=87)
FPG (mg/dL)		
Baseline (mean)	155.3	157.8
Change from baseline at Week 16 (adjusted mean‡)	−25.6	−10.4
Difference from placebo (adjusted mean‡) (95% CI)	−15.3§ (−21.4, −9.1)	

Change from baseline at Week 1 (adjusted mean‡)	−14.7	2.0
Body Weight (kg)		
Baseline (mean)	93.62	88.62
Change from baseline (adjusted mean‡)	−2.74	−0.86
Difference from placebo (adjusted mean‡) (95% CI)	−1.88# (−2.52, −1.24)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term

double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 vs. placebo + metformin.

¶ p-value <0.05 vs. placebo + metformin.

Percent change in body weight was analyzed as a key secondary endpoint (p-value <0.0001), absolute

body-weight change in kg was analyzed with a nominal p-value (p-value <0.001).

The proportion of patients who were discontinued for lack of glycemic control during the 16-week double-blind treatment period (adjusted for baseline HbA1c) was higher in the placebo twice daily plus metformin group (5.0%) than in the dapagliflozin 2.5 mg twice daily plus metformin group (1%). No patients in the dapagliflozin 5 mg twice daily plus metformin group discontinued due to inadequate glycemic control.

Active Glipizide-Controlled Study Add-On to Metformin Immediate-Release

A total of 816 patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, glipizide-controlled non-inferiority study with a 156-week extension period to evaluate dapagliflozin as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and dapagliflozin 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia.

Rescue for lack of glycemic control was not available in this study through Week 104, but was available between Weeks 105 and 208.

At the end of the titration period, 87% of patients treated with dapagliflozin had been titrated to the maximum study dose (10 mg), versus 73% treated with glipizide (20 mg). Dapagliflozin led to a similar mean reduction in HbA1c from baseline to Week 52, compared with glipizide, thus demonstrating non-inferiority (Table 9). Dapagliflozin treatment led to a significant mean reduction in body weight from baseline to week 52 compared with a mean increase in body weight in the glipizide group.

At Weeks 104 and 208, adjusted mean changes from baseline in HbA1c were −0.32% and −0.10%, and changes in body weight were −3.70 kg and −3.95 kg, respectively, for patients treated with dapagliflozin; adjusted mean changes from baseline in HbA1c were −0.14% and 0.20%, respectively, and changes in body weight were 1.36 kg and 1.12 kg, respectively, for patients treated with glipizide based on the longitudinal repeated measures analysis (Figures 5 and 6). The percent of patients achieving weight loss of ≥5% (adjusted) at Weeks 104 and 208 were 23.8% and 10.2%, respectively, for patients treated with dapagliflozin and 2.8% and 1.8%, respectively, for patients treated with glipizide.

By Weeks 52, 104, and 208, the proportion of patients who discontinued or were rescued for lack of glycemic control (adjusted for baseline HbA1c) were higher for glipizide plus metformin (3.6%, 21.6%, and 44.9%, respectively) than for XIGDUO plus metformin (0.2%, 14.5%, and 39.4%, respectively). At 52, 104, and 208 weeks, respectively, a significantly lower proportion of patients treated with dapagliflozin (3.5%, 4.3%, and 5.0%) experienced at least one event of hypoglycemia, compared to glipizide (40.8%, 47.0%, and 50.0%).

Table 9: Results at Week 52 (LOCF*) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-On to Metformin

Efficacy Parameter	**Dapagliflozin + Metformin N=400†**	**Glipizide + Metformin N=401†**
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline (adjusted mean‡)	−0.52	−0.52

Difference from glipizide + metformin (adjusted mean‡) (95% CI)	0.0§ (−0.11, 0.11)	
Body Weight (kg)		
Baseline (mean)	88.44	87.6
Change from baseline (adjusted mean‡)	−3.22	1.44
Difference from glipizide + metformin (adjusted mean‡) (95% CI)	−4.65¶ (−5.14, −4.17)	
Percent of patients achieving weight loss ≥5% (adjusted) (95%CI)	33.3%¶ (28.7, 37.9)	2.5% (1.0, 4.0)

* LOCF: last observation carried forward.

† Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ Noninferior to glipizide + metformin.

¶ p-value <0.0001

Figure 5: Adjusted Mean Change from Baseline Over Time in HbA1c (%)in a 208-Week Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis)

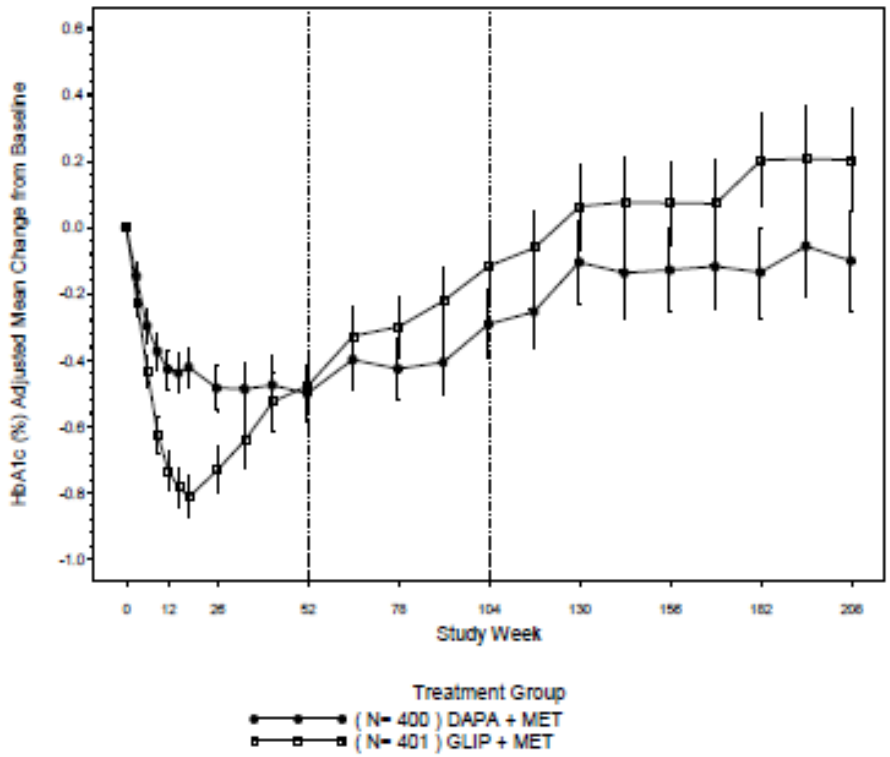
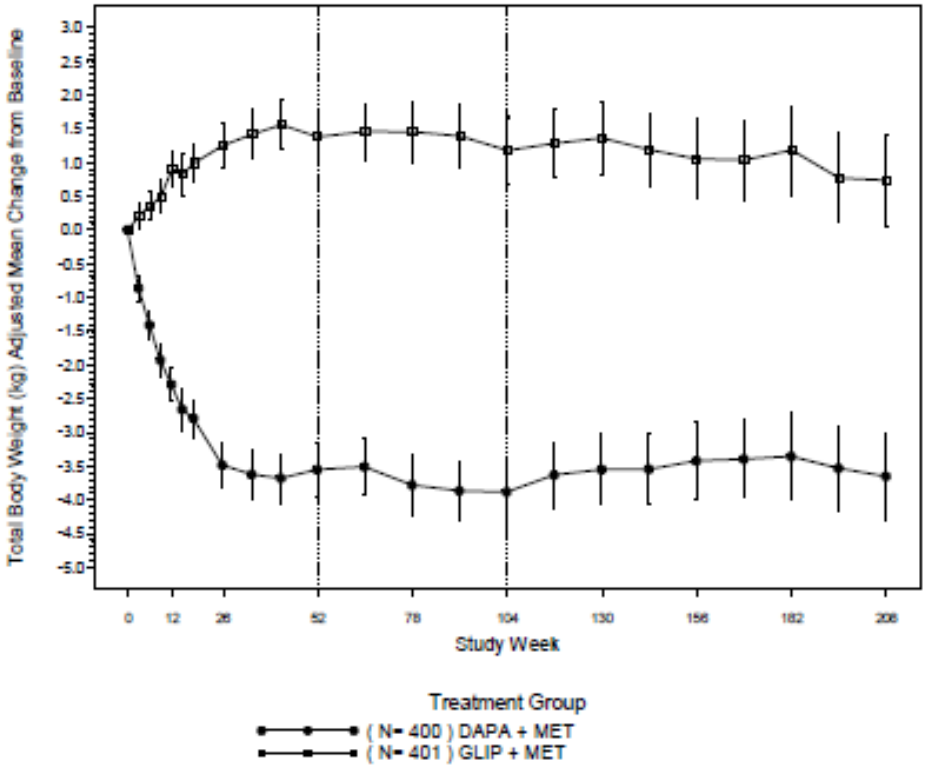


Figure 6: Adjusted Mean Change from Baseline Over Time in Body Weight (kg) in a 208-Week Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis)



Dapagliflozin Dual Energy X-ray Absorptiometry in Diabetic Patients

Due to the mechanism of action of dapagliflozin, a study was done to evaluate body composition and bone mineral density in 182 patients with type 2 diabetes. Treatment with dapagliflozin 10 mg added on to metformin IR over a 24-week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: −2.96 kg vs. −0.88 kg), waist circumference (mean change from baseline: −2.51 cm vs. −0.99 cm), and body-fat mass as measured by DXA (mean change from baseline −2.22 kg vs. −0.74 kg) rather than lean tissue or fluid loss. Dapagliflozin plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (mean change from baseline: −322.6 cm3 vs. −8.7 cm3) in a MRI substudy. Week 24 was analyzed using last observation carried forward (LOCF) analysis including data after rescue.

At Week 24, 2 patients (2.2%) in the placebo plus metformin group and no patients in the dapagliflozin 10 mg plus metformin group were rescued for lack of glycemic control.

At Week 50 and Week 102, improvements were sustained in the dapagliflozin 10 mg added on to metformin group compared with the placebo plus metformin group for body weight (adjusted mean change from baseline at Week 50: −4.39 kg vs. −2.03 kg; adjusted mean change from baseline at Week 102: −4.54 kg vs. −2.12 kg), waist circumference (adjusted mean change from baseline at Week 50: −5.0 cm vs. −3.0 cm; adjusted mean change from baseline at Week 102: −5.0 cm vs. −2.9 cm), and body-fat mass as measured by DXA at Week 102 (mean change from baseline: −2.80 kg vs. −1.46 kg) based on the longitudinal repeated measures analysis including data after rescue. In an MRI substudy at Weeks 50 and 102, dapagliflozin plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (adjusted mean change from baseline at Week 50: −120.0 cm3 vs. 61.5 cm3; adjusted mean change from baseline at Week 102: −214.9 cm3 vs. −22.3 cm3).

The proportion of patients at Week 50 (unadjusted for baseline HbA1c) and Week 102 (adjusted for baseline HbA1c) who were rescued or discontinued for lack of glycemic control was higher in the placebo plus metformin group (6.6% and 33.2%, respectively) than in the dapagliflozin 10 mg plus metformin group (2.2% and 13.5%, respectively). In an extension of this study to Week 50, there was no change in bone mineral density (BMD) for the lumbar spine, femoral neck, or total hip seen in either treatment group (mean decrease from baseline for all anatomical regions <0.5%). There was also no change in BMD in either treatment group up to Week 102 (mean decrease from baseline for all anatomical regions <1.0%). There were no clinically meaningful changes in markers of bone resorption or bone formation.

Use in Patients with Type 2 Diabetes and Moderate Renal Impairment

Dapagliflozin was assessed in two placebo-controlled studies of patients with type 2 diabetes and moderate renal impairment.

Patients with type 2 diabetes and an eGFR between 45 to less than 60 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy participated in a 24-week, double-blind, placebo-controlled clinical study (NCT02413398). Patients were randomized to either

dapagliflozin 10 mg or placebo, administered orally once daily. At Week 24, dapagliflozin provided statistically significant reductions in HbA1c compared with placebo (Table 10).

Table 10: Results at Week 24 of Placebo-Controlled Study for Dapagliflozin in Patients with Type 2 Diabetes and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m^2)

	Dapagliflozin 10 mg	**Placebo**
Number of patients:	**N=160**	**N=161**
HbA1c (%)		
Baseline (mean)	8.3	8.0
Change from baseline (adjusted mean*)	-0.4†	-0.1
Difference from placebo (adjusted mean*) (95% CI)	-0.3† (-0.5, - 0.1)	

* Least squares mean adjusted for baseline value; at Week 24, HbA1c was missing for 5.6% and 6.8% of individuals treated with dapagliflozin and placebo, respectively. Retrieved dropouts, i.e. observed HbA1c at Week 24 from subjects who discontinued treatment, were used to impute missing values in HbA1c.

† p-value <0.001 versus placebo

Cardiovascular and Renal Outcomes

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomised, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional cardiovascular risk factors (age ≥ 55 years in men or ≥ 60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use) or established cardiovascular disease.

Of 17,160 randomised patients, 6,974 (40.6%) had established cardiovascular disease and 10,186 (59.4%) did not have established cardiovascular disease. 8,582 patients were randomised to dapagliflozin 10 mg and 8,578 to placebo, and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female. In total, 22.4% had had diabetes for ≤ 5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR < 60 mL/min/1.73 m^2, and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ratio [UACR] ≥ 30 to ≤ 300 mg/g or > 300 mg/g, respectively).

Most patients (98%) used one or more diabetic medications at baseline, including metformin (82%), insulin (41%) and sulfonylurea (43%).

The primary endpoints were time to first event of the composite of cardiovascular death, myocardial infarction or ischaemic stroke (MACE) and time to first event of the composite of hospitalisation for heart failure or cardiovascular death. The secondary endpoints were a renal composite endpoint and all-cause mortality.

Major adverse cardiovascular events

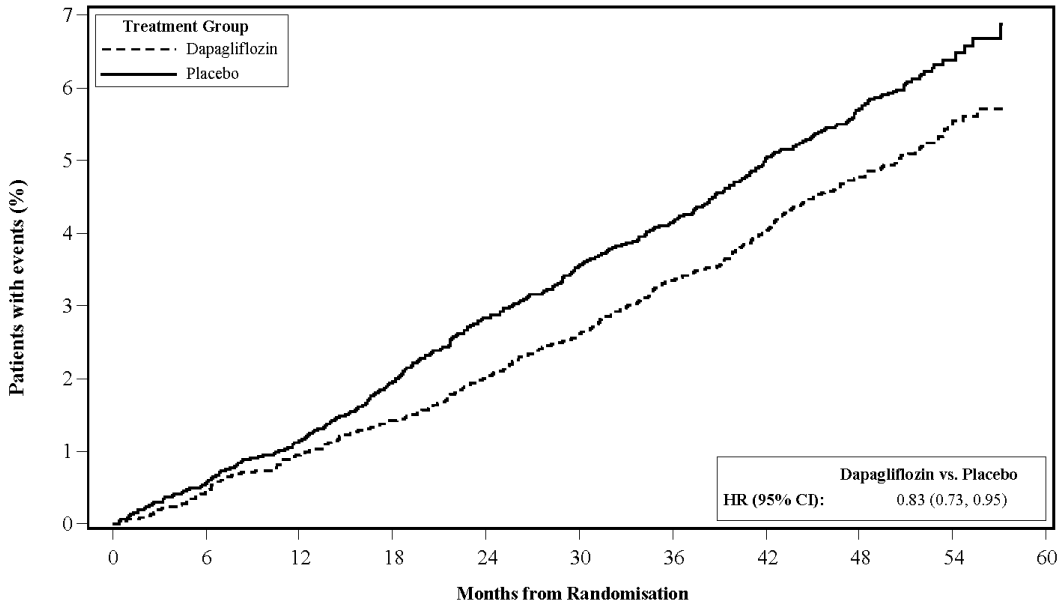
Dapagliflozin 10 mg demonstrated non-inferiority versus placebo for the composite of cardiovascular death, myocardial infarction or ischaemic stroke (one-sided $p < 0.001$).

Heart failure or cardiovascular death

Dapagliflozin 10 mg demonstrated superiority versus placebo in reducing the composite of hospitalisation for heart failure or cardiovascular death (Figure 7). The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death (Figure 8).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established cardiovascular disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR) and region.

Figure 7: Time to first occurrence of hospitalisation for heart failure or cardiovascular death



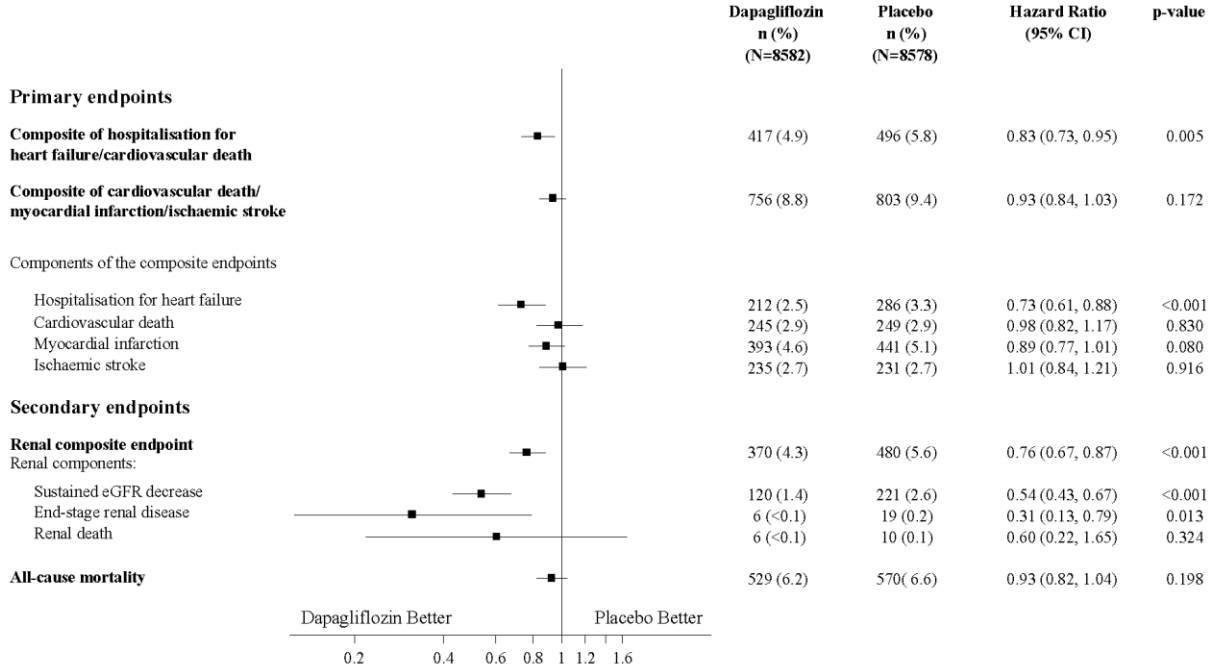
Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Patients at risk is the number of patients at risk at the beginning of the period.
HR=Hazard ratio CI=Confidence interval.

Results on primary and secondary endpoints are displayed in Figure 6. Superiority of dapagliflozin over placebo was not demonstrated for MACE (p= 0.172). The renal composite endpoint and all-cause mortality were therefore not tested as part of the confirmatory testing procedure.

Figure 8: Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components



Renal composite endpoint defined as: sustained confirmed ≥ 40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or end-stage renal disease (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m^2) and/or renal or cardiovascular death.
p-values are two-sided. p-values for the secondary endpoints and for single components are nominal. Time to first event was analysed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.
CI=confidence interval.

Nephropathy

Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, end-stage renal disease, renal or cardiovascular death. The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, end-stage renal disease and renal death (Figure 6).

The hazard ratio for time to nephropathy (sustained eGFR decrease, end-stage renal disease and renal death) was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

In addition, dapagliflozin reduced the new onset of sustained albuminuria (hazard ratio 0.79 [95% CI 0.72, 0.87]) and led to greater regression of macroalbuminuria (hazard ratio 1.82 [95% CI 1.51, 2.20]) compared with placebo.

Pharmacokinetic properties

XIGDUO XR combination tablets are considered to be bioequivalent to Co-administration of corresponding doses of dapagliflozin and metformin hydrochloride (XR and IR) administered together as individual tablets.

Interaction with food

XIGDUO XR

The administration of XIGDUO XR in healthy subjects after a standard meal compared to the fasted state results in the same extent of exposure for both dapagliflozin and metformin XR. Compared to the fasted state, the standard meal results in 35% reduction and a delay of 1 to 2 hours in the peak plasma concentrations of dapagliflozin. This effect of food is not considered to be clinically meaningful.

Absorption

Dapagliflozin

Dapagliflozin is rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (Cmax) are usually attained within 2 hours after administration in the fasted state. The Cmax and AUC values increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Metformin hydrochloride XR

Following a single oral dose of metformin extended-release, Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and Cmax are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 µg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively.

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein-Bound. Protein binding is not altered in various disease states (e.g., renal or hepatic impairment).

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time.

Metabolism

Dapagliflozin

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life (t1/2) for dapagliflozin is 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-Oglucuronide accounts for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma, accounting for 42% (based on AUC [0-12 h]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounts for >5% of the total plasma radioactivity. Dapagliflozin 3-Oglucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP mediated metabolism is a minor clearance pathway in humans.

Metformin hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which

less than 2% is unchanged dapagliflozin. After administration of 50 mg [14C]-dapagliflozin dose, 96% is recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose is excreted as parent drug.

Metformin hydrochloride

Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Specific Populations

Renal Impairment

XIGDUO XR

XIGDUO XR is contraindicated in patients with severe renal impairment (CrCl <30 ml/min/1.73 m^2) [see Contraindications and Special warning and special precautions for use]

Dapagliflozin

Dapagliflozin was evaluated in two studies that included patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m2, and an eGFR of 30 to less than 60 mL/min/1.73 m2) (see Clinical trial Information). The safety profile of dapagliflozin in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m2 was similar to the general population of patients with type 2 diabetes. Although patients in the dapagliflozin arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation.

For dosing recommendations for patients with moderate to severe renal impairment see section 4.2. At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60% and 87% higher, respectively, than those of patients with type 2 diabetes and normal renal function. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or 24-hour glucose excretion. The renal-glucose clearance and 24-hour

glucose excretion was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18, and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate, or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

In the DECLARE study, there were 3838 (44.7%) patients with eGFR 60 mL/min/1.73 m^2 to less than 90 mL/min/1.73 m^2 and 606 (7.1%) patients with eGFR below 60 mL/min/1.73 m^2. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function.

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

Dapagliflozin

For dosing recommendations for patients with moderate or severe hepatic impairment section 4.2. A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between patients with hepatic impairment compared to healthy subjects. In patients with mild or moderate hepatic impairment mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C), mean Cmax and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively. No dose adjustment is required for patients with severe hepatic impairment. However, the benefit risk for the use of dapagliflozin in patients with severe

hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment.

Age

Dapagliflozin

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies. The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI: 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI: 123, 129%). These differences in systemic exposure were considered to not be clinically meaningful.

In the DECLARE study, 3951 (46%) patients treated with dapagliflozin 10 mg were 65 years and older and 538 (6.3%) were 75 years and older. Safety and efficacy was similar for patients between 65 and below 75 years and those 75 years and above. The observed reduction in events of hospitalization for heart failure or cardiovascular death and findings on renal outcomes in these patients were consistent with the overall population.

Metformin hydrochloride

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and

Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric and Adolescent

Dapagliflozin

Pharmacokinetics in the pediatric and adolescent population have not been studied.

Metformin hydrochloride

After administration of a single oral metformin 500 mg tablet with food, geometric mean metformin Cmax and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Gender

Dapagliflozin

No dosage adjustment from the dose of 10 mg once daily is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUCss in females (n=619) was estimated to be 22% higher than in males (n=634), (90% CI: 117,124).

Metformin hydrochloride

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females**.**

Race

Dapagliflozin

No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (White, Black, or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to Whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range 3.7% lower, 1% higher). Compared to Whites, Black subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures [90% CI range 7.7% lower, 3.7% lower).

Metformin hydrochloride

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

Body Weight

No dose adjustments from the proposed dapagliflozin dose of 10 mg once daily is recommended on the basis of weight.

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high-body-weight subjects (≥120 kg, n=91) were estimated to be 78.3% (90% CI: 78.2, 83.2%) of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) is recommended.

Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low-body-weight subjects were estimated to be 29% higher than subjects with the reference group body weight. This difference is considered to be small, and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (<50 kg) is recommended.

Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in two year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were equivalent to AUC exposure multiples of approximately 72× (males) and 105× (females) the human AUC at MRHD of 10 mg/day. In rats, AUC exposures were approximately 131× (males) and 186× (females) the human AUC at the MRHD.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in an in-vitro clastogenicity assay, but only in the presence of S9 activation and at concentrations ≥ 100 µg/mL. Importantly, dapagliflozin was negative for clastogenicity in vivo in a series of studies

evaluating micronuclei or DNA repair in rats at exposure multiples >2100× the human exposure at the MRHD. These studies, along with the absence of tumor findings in the rat and mouse carcinogenicity studies, support that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin-related gene transcription changes were evaluated in kidney, liver, adipose, and skeletal muscle of Zucker Diabetic Fatty (ZDF) rats treated daily with dapagliflozin for 5 weeks. These organs were specifically selected as they represent target organs in the treatment of diabetes. There was no evidence that dapagliflozin caused transcriptional changes that are predictive of tumor promoters.

Dapagliflozin and its primary human metabolite (3-O-glucuronide) did not enhance the in vitro growth of six human urinary bladder transitional cell carcinomas (TCC) cell lines at concentrations ≥100× human Cmax at the MRHD. In a mouse xenograft study, dapagliflozin administered daily to male and female nude mice implanted with human TCC tumors did not significantly enhance the size of tumors at exposures up to 75× and up to 0.9× clinical exposures at the MRHD for dapagliflozin and its 3-O-glucuronide metabolite, respectively.

These studies provide evidence that dapagliflozin and its primary human metabolite do not enhance urinary bladder tumor growth.

In a 15-month phenotyping study, there was no evidence of any difference in survival, body weights, clinical pathology parameters, or histopathologic findings observed between SGLT2 KO mice and their wild-type (WT) counterparts. SGLT2 KO mice had glucosuria, unlike the WT mice. Despite a lifetime of glucosuria, there was no evidence of any alteration of renal function or proliferative changes observed in the kidneys or urinary bladders of SGLT2 KO mice. These data strongly suggest that high levels of urinary glucose do not induce urinary tract tumors or accelerate age-related urinary tract pathology.

In a study of fertility and early embryonic development in rats, doses of 15, 75, or 300/210 mg/kg/day dapagliflozin were administered to males (the 300 mg/kg/day dose was lowered to 210 mg/kg/day after 4 days); and doses of 3, 15, or 75 mg/kg/day were administered to females. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at any dose tested (at exposure multiples ≤1708× and 998× the MRHD in

males and females, respectively). However, at 300/210 mg/kg/day, seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were low numbers of morphologically abnormal sperm.

Metformin hydrochloride

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose of 2000 mg based on body-surface-area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body-surface-area comparisons.

Teratogenicity and impairment of early development

Dapagliflozin

Direct administration of dapagliflozin to weanling juvenile rats, and indirect exposure during late pregnancy and lactation (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation), are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥15× the MRHD. These findings were associated with dose-related increases in kidney weight and

macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1 month recovery period.

In a separate study of pre-natal and postnatal development, maternal rats were dosed from gestation day (GD) 6 through PND 21 (also at 1, 15, or 75 mg/kg/day), and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was again observed in adult offspring of treated dams, although only at 75 mg/kg/day (associated maternal and pup dapagliflozin exposures were 1415× and 137×, respectively, the human values at the MRHD). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥15 mg/kg/day (associated with pup exposures that are ≥29× the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day, and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity, 1 mg/kg/day, is associated with a maternal systemic exposure multiple that is approximately 19× the human value at the MRHD.

In additional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20,60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 1191× the MRHD. In rats, dapagliflozin was neither embryo lethal nor teratogenic at doses up to 75 mg/kg/day (1441× the MRHD). Doses ≥150 mg/kg/day (≥ 2344× the human values at the MRHD) were associated with both maternal and developmental toxicities. Maternal toxicity included mortality, adverse clinical signs, and decrements in body weight and food consumption. Developmental toxicity consisted of increased embryo-fetal lethality, increased incidences of fetal malformations and skeletal variations, and reduced fetal body weights. Malformations included a low incidence of great vessel malformations, fused ribs and vertebral centras, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This

represents an exposure of about 2 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Animal toxicology

A 3-month rat study was conducted with the combination of dapagliflozin and metformin. No toxicity was observed at AUC exposures 52 and 1.4 times the MRHD for dapagliflozin and metformin, respectively.

Dapagliflozin

Most of the effects observed in pivotal repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose and included decreases in body weights and/or body-weight gains, increased food consumption, and increases in urine volumes due to osmotic diuresis. Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤25 mg/kg/day (≥346× the human exposures at the MRHD) and in dogs for up to 12 months at doses of ≤120 mg/kg/day (≥3200× the human exposures at the MRHD). Also, single-dose studies with dapagliflozin indicated that the dapagliflozin 3-O-glucuronide metabolite would have been formed in both rat and dog toxicity studies at exposure levels (AUCs) that are greater than or approximately equal to anticipated human dapagliflozin 3-O-glucuronide exposures following administration of dapagliflozin at the MRHD. In rats, the most noteworthy nonclinical toxicity finding of increased trabecular bone and tissue mineralization (associated with increased serum calcium), was only observed at high-exposure multiples (≥2100× based on human exposures at the MRHD). Despite achieving exposure multiples of ≥3200× the human exposure at the MRHD, there was no dose-limiting or target-organ toxicities identified in the 12-month dog study.

Pharmaceutical Particulars

List of excipients

Metformin XR Layer

Carboxymethylcellulose Sodium

Hypromellose 2208

Hypromellose 2910

Microcrystalline Cellulose

Silicon Dioxide

Magnesium Stearate

Dapagliflozin Layer

Microcrystalline Cellulose

Lactose Anhydrous

Crospovidone

Silicon Dioxide

Magnesium Stearate

Film Coating Layer

Opadry II Orange 85F93339 (XIGDUO XR 5/500 mg)
Opadry II Pink 85F94592 (XIGDUO XR 5/1000 mg)
Opadry II Pink 85F94333 (XIGDUO XR 10/500 mg)
Opadry II Yellow 85F12372 (XIGDUO XR 10/1000 mg)

Incompatibilities

None

Shelf Life

Please refer to expiry date on outer carton.

Special precautions for storage

Store below 30°C

Pack size

XIGDUO XR 5 mg/500 mg: Box of 4 blisters @ 7 film-coated tablets (DKI1827900217A1)
XIGDUO XR 5 mg/1000 mg: Box of 4 blisters @ 7 film-coated tablets (DKI1827900217B1)
XIGDUO XR 10 mg/500 mg: Box of 4 blisters @ 7 film-coated tablets (DKI1827900217C1)
XIGDUO XR 10 mg/1000 mg: Box of 4 blisters @ 7 film-coated tablets (DKI1827900217D1)

Golongan Obat Keras

HARUS DENGAN RESEP DOKTER

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