**XIGDUO XR (dapagliflozin and metformin hydrochloride extended-release) tablets, for oral use**
**Xigduo XR 5mg/500mg extended-release tablets**
**Xigduo XR 5mg/1000mg extended-release tablets**
**Xigduo XR 10mg/500mg extended-release tablets**
**Xigduo XR 10mg/1000mg extended-release tablets**

**WARNING: LACTIC ACIDOSIS**

- **Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin-associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL *[see Warnings and Precautions (5.1)]*.**
- **Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment.**
- **Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the full prescribing information *[see Dosage and Administration (2.2), Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7), and Use in Specific Populations (8.6, 8.7)]*.**
- **If metformin-associated lactic acidosis is suspected, immediately discontinue XIGDUO XR and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended *[see Warnings and Precautions (5.1)]*.**

## 1 INDICATION AND USAGE

XIGDUO XR (dapagliflozin and metformin hydrochloride extended-release) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate [see *Clinical Studies (14)*].

### 1.1 Limitations of Use

XIGDUO XR is not recommended for patients with type 1 diabetes mellitus or diabetic ketoacidosis.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Prior to Initiation of XIGDUO XR

- Assess renal function before initiating XIGDUO XR therapy and periodically thereafter *[see Warnings and Precautions (5.1, 5.4)]*.
- In patients with volume depletion, correct this condition prior to initiation of XIGDUO XR *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5)*

### 2.2 Recommended Dosage

- Take Xigduo XR once daily in the morning with food with gradual dose escalation to reduce the gastrointestinal (GI) side effects due to metformin.
- Swallow XIGDUO XR tablets whole and never crush, cut, or chew. Occasionally, the inactive ingredients of XIGDUO XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.
- Individualize the starting dose of XIGDUO XR based upon the patient's current regimen
- 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 hydrochloride.
- Patients taking an evening dose of metformin XR should skip their last dose before starting XIGDUO XR.

- In patients with volume depletion, correcting this condition prior to initiation of XIGDUO XR is recommended [see *Warnings and Precautions (5.4)*, *Use in Specific Populations (8.5)*, and *Patient Counseling Information (17)*].

### 2.3 Patients with Renal Impairment

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

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

## 3 DOSAGE FORMS AND STRENGTHS

XIGDUO XR (dapagliflozin and metformin hydrochloride ) extended-release. tablets are available as follows:

| Dapagliflozin Strength | Metformin hydrochloride Strength | Color/Shape | Tablet Markings |
|---|---|---|---|
| 5 mg | 500 mg | orange, biconvex, capsule-shaped, and film-coated tablet | "1070" and "5/500" debossed on one side and plain on the reverse side |
| 5 mg | 1,000 mg | pink to dark pink, biconvex, oval-shaped, and film-coated tablet | "1071" and "5/1000" debossed on one side and plain on the reverse side |
| 10 mg | 500 mg | pink, biconvex, capsule-shaped, and film-coated tablet | "1072" and "10/500" debossed on one side and plain on the reverse side |
| 10 mg | 1,000 mg | yellow to dark yellow, biconvex, oval-shaped, and film-coated tablet | "1073" and "10/1000" debossed on one side and plain on the reverse side |

## 4 CONTRAINDICATIONS

XIGDUO XR is contraindicated in patients with:

- severe renal impairment (eGFR below 30 mL/min/1.73 $m^2$ end stage renal disease or patients on dialysis [see *Warnings and Precautions (5.1)*].
- History of a serious hypersensitivity reaction to dapagliflozin such as anaphylactic reactions or angioedema or hypersensitivity to metformin hydrochloride [see *Adverse Reactions (6.1)*].
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin *[see Warnings and Precautions (5.1) and Warnings and Precautions (5.2)]*.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Lactic Acidosis

There have been post-marketing cases of metformin-associated lactic acidosis,

including fatal cases. These cases

had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence, ; however, hypothermia, hypotension, and resistant bradyarrhythmias have occurred with severe acidosis

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5mmol/L), anion gap acidosis (without evidence of (ketonuria or ketonemia).

), and an increased lactate: pyruvate ratio; metformin plasma levels generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted. promptly in a hospital setting, along with immediate discontinuation of XIGDUO XR.

In XIGDUO XR-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin. (metformin hydrochloride is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue XIGDUO XR and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associated lactic acidosis are provided below:

*Renal Impairment:* The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include *[see Dosage and Administration (2.1 and 2.4) and Clinical Pharmacology (12.3)]*:

- Before initiating XIGDUO XR, obtain an estimated glomerular filtration rate (eGFR).
- XIGDUO XR is contraindicated in patients with an eGFR less than 30 mL/min/1.73 $m^2$ *[see Contraindications (4)]*.
- Obtain an eGFR at least annually in all patients taking XIGDUO XR. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

*Drug Interactions:* The concomitant use of XIGDUO XR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs) *[see Drug Interactions (7)]*. Therefore, consider more frequent monitoring of patients.

*Age 65 or Greater:* The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than

younger patients. Assess renal function more frequently in elderly patients *[see Use in Specific Populations (8.5)]*.

*Radiological Studies with Contrast:* Administration of intravascular iodinated contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lactic acidosis. Stop XIGDUO XR at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart XIGDUO XR if renal function is stable.

*Surgery and Other Procedures:* Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. XIGDUO XR should be temporarily discontinued while patients have restricted food and fluid intake.

**Hypoxic States *:* Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur , discontinue XIGDUO XR.**

*Excessive Alcohol Intake:* Alcohol potentiates the effect of metformin on lactate metabolism, and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving XIGDUO XR.

Hepatic Impairment: Patients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of XIGDUO XR in patients with clinical or laboratory evidence of hepatic disease.

## 5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus taking sodium glucose co-transporter-2 (SGLT2) inhibitors, including dapagliflozin *[see*

*(6.1)]*.. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin XIGDUO XR is not indicated for the treatment of patients with type 1 diabetes mellitus [see *Indications and Usage (1.1)*].

Patients treated with XIGDUO XR who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as ketoacidsosis associated with XIGDUO XR may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, XIGDUO XR should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating XIGDUO XR, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse. For patients who undergo scheduled surgery, consider temporarily discontinuing XIGDUO XR for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)].*

Consider monitoring for ketoacidosis and temporarily discontinuing XIGDUO XR in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting XIGDUO XR.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue XIGDUO XR and seek medical attention immediately if signs and symptoms occur.

## 5.3 Volume Depletion

Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 $m^2$), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating XIGDUO XR in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension and renal function after initiating therapy.

### 5.4 Urosepsis and Pyelonephritis

Serous urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including dapagliflozin. 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 *Adverse Reactions (6.2)*].

### 5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. XIGDUO XR may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with XIGDUO XR *[see Drug Interactions (7)]*.

### 5.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with XIGDUO XR presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue XIGDUO XR, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

### 5.7 Vitamin $B_{12}$ Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin $B_{12}$ levels, without clinical manifestations, was observed in approximately 7% of patients. such decrease, possibly due to interference with $B_{12}$ absorption from the $B_{12}$-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin $B_{12}$ supplementation.

Certain individuals (those with inadequate vitamin $B_{12}$ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin $B_{12}$ levels. Measure hematologic parameters on an annual basis and vitamin $B_{12}$ at 2- to 3-year intervals in patients on XIGDUO XR and manage any abnormalities *[see Adverse Reactions (6.1)]*.

### 5.8 Genital Mycotic Infections

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections [see *Adverse Reactions (6.1)*]. Monitor and treat appropriately.

## 6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Ketoacidosis [*see Warnings and Precautions (5.2)*]
- Volume Depletion [see Warnings and Precautions (5.3)]
- 
- Urosepsis and Pyelonephritis [*see Warnings and Precautions (5.4)*]
- Use with Medications Known to Cause Hypoglycemia [see *Warnings and Precautions (5.5)*]
  - Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.6)]*
- Vitamin $B_{12}$ Concentrations [see *Warnings and Precautions (5.7)*]
- Genital Mycotic Infections [see *Warnings and Precautions (5.8)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

*Dapagliflozin and Metformin hydrochloride*

Data from a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin coadministered with metformin immediate- or extended-release was used to evaluate safety. This pool included several add-on studies (metformin alone and in combination with a dipeptidyl peptidase-4 [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 mellitus 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%).

Table 1 shows common adverse reactions associated with the use of dapagliflozin and metformin. These adverse reactions were not present at baseline, occurred more commonly on dapagliflozin and metformin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

**Table 1: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin and Metformin**

| Adverse Reaction | % of Patients | | |
|---|---|---|---|
| | Pool of 8 Placebo-Controlled Studies | | |
| | Placebo and Metformin N=1185 | Dapagliflozin 5 mg and Metformin N=410 | Dapagliflozin 10 mg and Metformin N=983 |
| Female genital mycotic infections[1] | 1.5 | 9.4 | 9.3 |
| Nasopharyngitis | 5.9 | 6.3 | 5.2 |
| Urinary tract infections[2] | 3.6 | 6.1 | 5.5 |
| Diarrhea | 5.6 | 5.9 | 4.2 |
| Headache | 2.8 | 5.4 | 3.3 |
| Male genital mycotic infections[3] | 0 | 4.3 | 3.6 |
| Influenza | 2.4 | 4.1 | 2.6 |
| Nausea | 2.0 | 3.9 | 2.6 |
| **Adverse Reaction** | **% of Patients** | | |
| | **Pool of 8 Placebo-Controlled Studies** | | |
| | **Placebo and Metformin N=1185** | **Dapagliflozin 5 mg and Metformin N=410** | **Dapagliflozin 10 mg and Metformin N=983** |
| Back pain | 3.2 | 3.4 | 2.5 |
| Dizziness | 2.2 | 3.2 | 1.8 |
| Cough | 1.9 | 3.2 | 1.4 |
| Constipation | 1.6 | 2.9 | 1.9 |
| Dyslipidemia | 1.4 | 2.7 | 1.5 |
| Pharyngitis | 1.1 | 2.7 | 1.5 |
| Increased urination[4] | 1.4 | 2.4 | 2.6 |
| Discomfort with urination | 1.1 | 2.2 | 1.6 |

1. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, genital infection, vulvovaginitis, fungal genital infection, vulvovaginal candidiasis, vulval abscess, genital candidiasis, and vaginitis bacterial. (N for females: Placebo and metformin=534, dapagliflozin 5 mg and metformin=223, dapagliflozin 10 mg and metformin=430).
2. Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, pyelonephritis, urethritis, and prostatitis.
3. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, balanoposthitis. (N

for males: Placebo and metformin=651, dapagliflozin 5 mg and metformin=187, dapagliflozin 10 mg and metformin=553).

4. Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

*Metformin hydrochloride*

In placebo-controlled monotherapy trials of metformin extended-release, diarrhea and nausea/vomiting were reported in >5% of metformin-treated patients and more commonly than in placebo-treated patients (9.6% versus 2.6% for diarrhea and 6.5% versus 1.5% for nausea/vomiting). Diarrhea led to discontinuation of study medication in 0.6% of the patients treated with metformin extended-release.

**Pool of 12 Placebo-Controlled Studies for Dapagliflozin 5 and 10 mg**

*Dapagliflozin*

The data in Table 2 are derived from 12 glycemic control placebo-controlled studies ranging from 12 to 24 weeks. In 4 studies dapagliflozin was used as monotherapy, and in 8 studies dapagliflozin was used as add-on to background antidiabetic therapy or as combination therapy with metformin [see *Clinical Studies (14.1)*].

These data reflect exposure of 2338 patients to dapagliflozin with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), dapagliflozin 5 mg (N=1145), or dapagliflozin 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean HbA1c of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 $m^2$).

Table 2 shows common adverse reactions associated with the use of dapagliflozin. These adverse reactions were not present at baseline, occurred more commonly on dapagliflozin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

**Table 2: Adverse Reactions in Placebo- Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with Dapagliflozin**

| Adverse Reaction | % of Patients | | |
|---|---|---|---|
| | Pool of 12 Placebo-Controlled Studies | | |
| | Placebo N=1393 | Dapagliflozin 5 mg N=1145 | Dapagliflozin 10 mg N=1193 |
| Female genital mycotic infections[1] | 1.5 | 8.4 | 6.9 |
| Nasopharyngitis | 6.2 | 6.6 | 6.3 |
| Urinary tract infections[2] | 3.7 | 5.7 | 4.3 |
| Back pain | 3.2 | 3.1 | 4.2 |
| Increased urination[3] | 1.7 | 2.9 | 3.8 |
| Male genital mycotic infections[4] | 0.3 | 2.8 | 2.7 |

| | | | |
|---|---|---|---|
| Nausea | 2.4 | 2.8 | 2.5 |
| Influenza | 2.3 | 2.7 | 2.3 |
| Dyslipidemia | 1.5 | 2.1 | 2.5 |
| Constipation | 1.5 | 2.2 | 1.9 |
| Discomfort with urination | 0.7 | 1.6 | 2.1 |
| Pain in extremity | 1.4 | 2.0 | 1.7 |

1. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, dapagliflozin 5 mg=581, dapagliflozin 10 mg=598).
2. Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.
3. Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.
4. Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis. (N for males: Placebo=716, dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

### Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg

dapagliflozin 10 mg was also evaluated in a larger glycemic control placebo-controlled study pool. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with dapagliflozin 10 mg for 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 were 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, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 $m^2$).

### Volume Depletion

Dapagliflozin causes an osmotic diuresis, which may lead to reductions in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) are shown in Table 3 for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study [see *Warnings and Precautions (5.2)*].

**Table 3: Adverse Reactions Related to Volume Depletion[1] 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<br>5<br>(0.4%) | N=1145<br>7<br>(0.6%) | N=1193<br>9<br>(0.8%) | N=2295<br>17<br>(0.7%) | N=2360<br>27<br>(1.1%) | N=8569<br>207<br>(2.4%) | N=8574<br>213<br>(2.5%) |
| **Patient Subgroup n (%)** | | | | | | | |
| Patients on loop diuretics | n=55<br>1<br>(1.8%) | n=40<br>0 | n=31<br>3<br>(9.7%) | n=267<br>4<br>(1.5%) | n=236<br>6<br>(2.5%) | n=934<br>57<br>(6.1%) | n=866<br>57<br>(6.6%) |
| Patients with moderate renal impairment with eGFR ≥≥30 and <60 mL/min/1.73 $m^2$ | n=107<br>2<br>(1.9%) | n=107<br>1<br>(0.9%) | n=89<br>1<br>(1.1%) | n=268<br>4<br>(1.5%) | n=265<br>5<br>(1.9%) | n=658<br>30<br>(4.6%) | n=604<br>35<br>(5.8%) |
| Patients ≥≥65 years of age | n=276<br>1<br>(0.4%) | n=216<br>1<br>(0.5%) | n=204<br>3<br>(1.5%) | n=711<br>6<br>(0.8%) | n=665<br>11<br>(1.7%) | n=3950<br>121<br>(3.1%) | n=3948<br>117<br>(3.0%) |

[1] Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

### Hypoglycemia

The frequency of hypoglycemia by study [see *Clinical Studies (14.1)*] is shown in Table 4. Hypoglycemia was more frequent when dapagliflozin was added to sulfonylurea or insulin [see *Warnings and Precautions (5.5)*].

**Table 4: Incidence of severe Hypoglycemia and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies**

| | Placebo | Dapagliflozin 5 mg | Dapagliflozin 10 mg |
|---|---|---|---|
| **Add-on to Metformin[1] (24 weeks)** | **N=137** | **N=137** | **N=135** |

| | | | |
|---|---|---|---|
| Major [n (%)] | 0 | 0 | 0 |
| Minor [n (%)] | 0 | 2 (1.5) | 1 (0.7) |
| **Active Control Add-on to Metformin versus Glipizide (52 weeks)** | **N=408** | – | **N=406** |
| Major [n (%)] | 3 (0.7) | – | 0 |
| Minor [n (%)] | 147 (36.0) | – | 7 (1.7) |
| | **Placebo** | **Dapagliflozin 5 mg** | **Dapagliflozin 10 mg** |
| **Add-on to DPP4 inhibitor (with or without Metformin) (24 weeks)** | **N=226** | – | **N=225** |
| Major [n (%)] | 0 | – | 1 (0.4) |
| Minor [n (%)] | 3 (1.3) | – | 4 (1.8) |
| **Add-on to Insulin with or without other OADs‡ (24 weeks)** | **N=197** | **N=212** | **N=196** |
| Major [n (%)] | 1 (0.5) | 1 (0.5) | 1 (0.5) |
| Minor [n (%)] | 67 (34.0) | 92 (43.4) | 79 (40.3) |

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose < 54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study *[see Clinical Studies (14.2)]*, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with dapagliflozin 10 mg and 83 (1.0%) out of 8569 patients treated with placebo.

### Genital Mycotic Infections

In the glycemic control studies, genital mycotic infections were more frequent with dapagliflozin treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on dapagliflozin 5 mg, and 4.8% on dapagliflozin 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with dapagliflozin 10 mg. Infections were more frequently reported in females than in males (see Table 2). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively). In the DECLARE study *[see Clinical Studies (14.2)]*, serious genital mycotic infections were reported in <0.1% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo.

### Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with dapagliflozin treatment. In glycemic control studies, , serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of dapagliflozin-treated patients. If hypersensitivity reactions occur, discontinue use of dapagliflozin; treat per standard of care and monitor until signs and symptoms resolve.

## Ketoacidosis

In the DECLARE study *[see Warnings and Precautions (5.2) and Clinical Studies (14.2)]*, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the dapagliflozin-treated group and in 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

### Laboratory Tests

***Increases in Serum Creatinine and Decreases in eGFR***

*Dapagliflozin*

Initiation of SGLT2 inhibitors, including dapagliflozin, causes a small increase in serum creatinine and decrease in eGFR. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions (5.3)]*. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with dapagliflozin.

***Increase in Hematocrit***

*Dapagliflozin*

In the pool of 13 placebo-controlled studies of glycemic control, , 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 −0.33% in the placebo group and 2.30% in the dapagliflozin 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of dapagliflozin 10 mg–treated patients.

***Increase in Low-Density Lipoprotein Cholesterol***

***Dapagliflozin***

In the pool of 13 placebo-controlled studies of glycemic control, , changes from baseline in mean lipid values were reported in dapagliflozintreated patients compared to placebo-treated patients. Mean percent change from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol and −1.0% versus 2.9% for LDL cholesterol in the placebo and dapagliflozin 10 mg groups, respectively. In the DECLARE study [see Clinical Studies (14.2)], 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 $B_{12}$ Concentrations***

*Metformin hydrochloride*

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously

normal serum vitamin B12 levels was observed in approximately 7% of patients.

## 6.2 Post-marketing Experience

Dapagliflozin

Additional adverse reactions have been identified during post approval 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
  - Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)
  - Rash

*Metformin hydrochloride*

- Cholestatic, hepatocellular, and mixed hepatocellular liver injury

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

# 7 DRUG INTERACTIONS

**Table 5: Clinically Relevant Interactions with XIGDUO XR**

| **Carbonic Anhydrase Inhibitors** |
|---|

**Table 5: Clinically Relevant Interactions with XIGDUO XR**

| | |
|---|---|
| Clinical Impact | Topiramate or other carbonic anhydrase inhibitors (e.g., zonisamide, acetazolamide or dichlorphenamide) frequently causes a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with XIGDUO XR may increase the risk for lactic acidosis. |
| Intervention | Consider more frequent monitoring of these patients. |
| **Drugs that Reduce Metformin Clearance** | |
| Clinical Impact | Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors, such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis *[see Clinical Pharmacology (12.3)]*. |
| Intervention | Consider the benefits and risks of concomitant use. |
| **Alcohol** | |
| Clinical Impact | Alcohol is known to potentiate the effect of metformin on lactate metabolism. |
| Intervention | Warn patients against excessive alcohol intake while receiving XIGDUO XR. |
| **Insulin or Insulin Secretagogues** | |
| *Clinical Impact* | The risk of hypoglycemia may be increased when XIGDUO XR is used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea) *[see Warnings and Precautions (5.5)]*. |
| *Intervention* | Concomitant use may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia. |
| **Drugs Affecting Glycemic Control** | |
| Clinical Impact | Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. |
| Intervention | When such drugs are administered to a patient receiving XIGDUO XR, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving XIGDUO XR, observe the patient closely for hypoglycemia. |
| **Lithium** | |
| *Clinical Impact* | Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations |
| *Intervention* | Monitor serum lithium concentration more frequently during XIGDUO XR initiation and dosage changes. |
| **Positive Urine Glucose Test** | |
| Clinical Impact | SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. |
| Intervention | Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control. |
| **Interference with 1,5-anhydroglucitol (1,5-AG) Assay** | |
| Clinical Impact | Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. |
| Intervention | Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control. |

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, XIGDUO XR is not recommended during the second and third trimesters of pregnancy.

Limited data with XIGDUO XR or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk *(see Data)*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to Based on animal data showing adverse renal effects, XIGDUO XR is not recommended during the second and third trimesters of pregnancy,

at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

*Disease-associated maternal and/or embryofetal risk*

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

*Human Data*

Published data from post-marketing studies have not reported a clear association with metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when metformin was

used during pregnancy

However, these studies cannot definitely establish the absence of any metformin-associated risk because of methodological limitations, including small sample size and inconsistent comparator groups.

*Animal Data*

*Dapagliflozin*

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15 times the 10mg clinical dose, (based on AUC.) The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the aa 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415 times and 137 times, respectively, the human values at the 10mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greated or equal to 29 times the 10mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day, (19 times the 10mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy in rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441 times the 10mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only. At higher dosages, equal to or greater than 150 mg/kg 2344 times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed.

in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

*Metformin hydrochloride*

Metformin hydrochloride did not cause adverse developmental effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2 and 6 times a 2000 mg clinical dose based on body surface area ($mg/m^2$) for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

## 8.2 Lactation

Risk Summary

There no information regarding the presence of XIGDUO XR or dapaglifozin in human milk. the effects on the breastfed infant, or the effects on milk production.

Limited published studies report that metformin is present in human milk *(see Data)*. However, there is insufficient information on the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production. Dapagliflozin is present in the milk of lactating rats.

*(see Data).* However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of XIGDUO XR is not recommended while breastfeeding.

Data

*Dapagliflozin*

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49 indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile

rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

*Metformin hydrochloride*

Published clinical lactation studies report that metformin is present in human milk which resulted in infant doses approximately 0.11% to 1% of the maternal weight-adjusted dosage and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin during lactation because of small sample size and limited adverse event data collected in infants.

## 8.3 Females and Males of Reproductive Potential

Discuss the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some anovulatory women.

## 8.4 Pediatric Use

Safety and effectiveness of XIGDUO XR in pediatric patients under 18 years of age have not been established.

## 8.5 Geriatric Use

*XIGDUO XR*

No XIGDUO XR dosage change is recommended based on age. . More frequent assessment of renal function is recommended in elderly patients.

*Dapagliflozin*

A total of 1424 (24%) of the 5936 dapagliflozin-treated patients were 65 years and over and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of dapagliflozin in improving glycemic control. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure compared to patients treated with placebo [see *Warnings and Precautions (5.4)* and *Adverse Reactions (6.1)*].

*Metformin hydrochloride*

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of lactic acidosis with metformin is greater in patients with moderately to severely impaired renal function, XIGDUO XR should only be used in patients with normal or mildly impaired renal function. 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 should be based on a careful assessment of renal function [see *Contraindications (4)*, *Warnings and Precautions (5.1, 5.3)*, and *Clinical Pharmacology (12.3)*].

## 8.6 Renal Impairment

Initiation of XIGDUO XR is not recommended in patients with an eGFR below 45 mL/min/1.73 $m^2$ and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 $m^2$), end stage renal disease or patients on dialysis*[see Dosage and Administration (2.4), Contraindications (4) and Warnings and Precautions (5.1, 5.3)]*.

*Dapagliflozin*

Dapagliflozin 10 mg was evaluated in two glycemic control studies that included patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 $m^2$, and an eGFR of 30 to less than 60 mL/min/1.73 $m^2$) *[see Clinical Studies (14.1)]*. Patients with diabetes and renal impairment using dapagliflozin 10 mg are more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 $m^2$, 13 patients receiving dapagliflozin experienced bone fractures compared to none receiving placebo. Use of dapagliflozin 10 mg for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 $m^2$ *[see Dosage and Administration (2.4)]*.

*Metformin hydrochloride*

Metformin is substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of renal impairment. XIGDUO XR is contraindicated in severe renal impairment, patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 $m^2$ *[see Dosage and Administration (2.3), Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.2)]*.

## 8.7 Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. XIGDUO XR is not recommended in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

## 9 OVERDOSAGE

*Dapagliflozin*

In the event of an overdose, contact the Poison Control Center. The removal of dapagliflozin by hemodialysis has not been studied.

*Metformin hydrochloride*

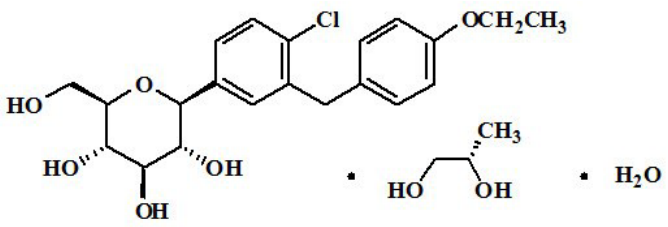
Overdose of metformin hydrochloride has occurred, including ingestion of amounts >50 grams.. Lactic acidosis has been reported in approximately 32% of metformin overdose cases [see *Warnings and Precautions (5.1)*]. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

## 10 DESCRIPTION

XIGDUO XR tablets contain: dapagliflozin , a SGLT2 inhibitor, and metformin hydrochloride , a biguanide.

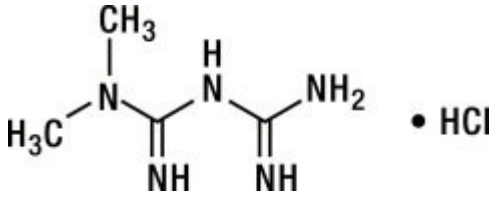
*Dapagliflozin*

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the formula weight is 502.98. The structural formula is:



*Metformin hydrochloride*

Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The $pK_a$ of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:




*XIGDUO XR*

XIGDUO XR is available for oral administration as tablets containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 5 mg/500 mg), the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 5 mg/1000 mg), the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 500 mg metformin hydrochloride (XIGDUO XR 10 mg/500 mg), or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol and 1000 mg metformin hydrochloride (XIGDUO XR 10 mg/1000 mg).

Each film-coated tablet of XIGDUO XR contains the following inactive ingredients: microcrystalline cellulose PH302, lactose anhydrous, crospovidone, silicon dioxide, magnesium stearate, carboxymethylcellulose sodium, and hypromellose 2208. The 5 mg/500 mg and 10 mg/500 mg strength tablets of XIGDUO XR also contain microcrystalline cellulose PH102 and hypromellose 2910.

The film coatings contain the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. Additionally, the film coating for the XIGDUO XR 5 mg/500 mg tablets contains FD&C Yellow No. 6/Sunset Yellow FCF aluminum lake and the film coating for the XIGDUO XR 5 mg/1000 mg, 10 mg/500 mg, and 10 mg/1000 mg tablets contains iron oxides.

# 11 CLINICAL PHARMACOLOGY

## 11.1 Mechanism of Action

*Dapagliflozin*

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose, and thereby promotes urinary glucose excretion. , Dapagliflozin also reduces sodium

reabsorption and increases the delivery of sodium to the distal tubule. This may influence several

physiological functions including, but not restricted to, lowering both pre- and afterload of the

heart and downregulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubule-glomerular feedback.

*Metformin hydrochloride*

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, 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. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

## 11.2 Pharmacodynamics

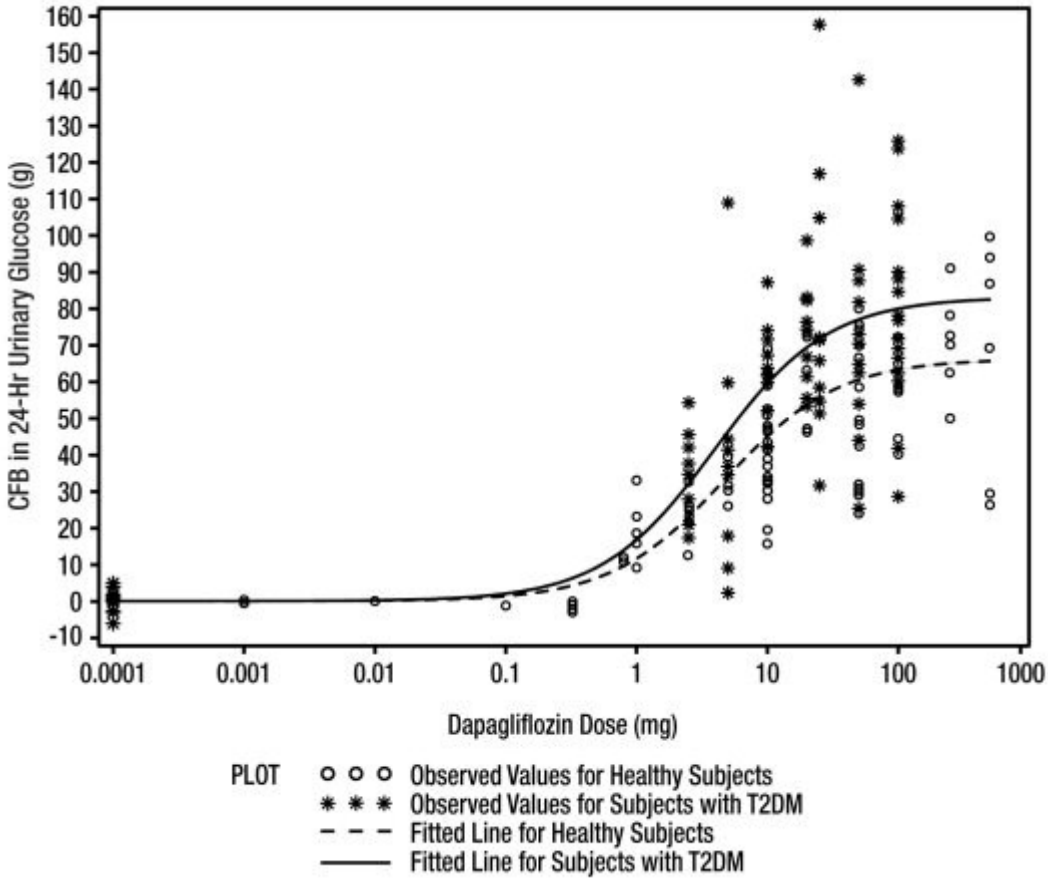
### General

*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 (see Figure 1). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume [see *Adverse Reactions (6.1)*]. After discontinuation of dapagliflozin, on average, the elevation in urinary

glucose excretion approaches baseline by about 3 days for the 10 mg dose.

**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.

## 11.3 Pharmacokinetics

*XIGDUO XR*

The administration of XIGDUO XR in healthy subjects after a standard meal compared to the fasted state resulted in the same extent of exposure for both dapagliflozin and metformin extended-release. Compared to the fasted state, the standard meal resulted 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. Food has no relevant effect on the pharmacokinetics of metformin when administered as XIGDUO XR combination tablets.

**Absorption**

*Dapagliflozin*

Following oral administration of dapagliflozin, the maximum plasma concentration ($C_{max}$) is usually attained within 2 hours under fasting state. The $C_{max}$ and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is
78%. Administration of dapagliflozin with a high-fat meal decreases its $C_{max}$ by up to 50% and prolongs $T_{max}$ by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

*Metformin hydrochloride*

Following a single oral dose of metformin extended-release, $C_{max}$ is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on $C_{max}$ and $T_{max}$ of metformin.

**Distribution**

*Dapagliflozin*

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with 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.

**Metabolism**

*Dapagliflozin*

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

*Metformin hydrochloride*

Intravenous single-dose studies in healthy 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 the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

*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*

*Dapagliflozin*

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes mellitus with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 100%, and 200% higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes mellitus and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patients with type 2 diabetes mellitus with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.3)*, and *Use in Specific Populations (8.6)*] and Clinical studies (14).

*Metformin hydrochloride*

In patients with decreased renal function the plasma and blood half-life of metformin is prolonged, and the renal clearance is decreased [see Contraindications (4) and Warnings and Precautions (5.1)].

#### *Hepatic Impairment*

*Dapagliflozin*

In patients with mild and moderate hepatic impairment (Child-Pugh Classes A and B), mean $C_{max}$ and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh Class C), mean $C_{max}$ and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

*Metformin hydrochloride*

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment *[see Warnings and Precautions (5.1)]*.

***Geriatric***

*Dapagliflozin*

Based on a population pharmacokinetic analysis, age does not have a clinically meaningful effect on systemic exposures of dapagliflozin.

*Metformin hydrochloride*

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggests that total plasma clearance of metformin is decreased, the half-life is prolonged, and $C_{max}$ 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***

Pharmacokinetics of XIGDUO XR in the pediatric population has not been studied.

***Gender***

*Dapagliflozin*

Based on a population pharmacokinetic analysis, gender does not have a clinically meaningful effect on systemic exposures of dapagliflozin.

*Metformin hydrochloride*

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes mellitus 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*

Based on a population pharmacokinetic analysis, race (White, Black, or Asian) does not have a clinically meaningful effect on systemic exposures of dapagliflozin.

*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 mellitus, the antihyperglycemic effect was comparable in Whites (n=249), Blacks (n=51), and Hispanics (n=24).

***Body Weight***

*Dapagliflozin*

Based on a population pharmacokinetic analysis, body weight does not have a clinically meaningful effect on systemic exposures of dapagliflozin.

### Drug Interactions

Specific pharmacokinetic drug interaction studies with XIGDUO XR have not been performed, although such studies have been conducted with the individual dapagliflozin and metformin components.

#### *In Vitro Assessment of Drug Interactions*

*Dapagliflozin*

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP 1A2, 2B6, or 3A4. 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-Oglucuronide 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.

#### *Effects of Other Drugs on Metformin*

Table 6 shows the effect of other co-administered drugs on metformin.

**Table 6: Effect of Co-administered Drug on Plasma Metformin Systemic Exposure**

| Co-administered Drug (Dose Regimen)[1] | Metformin (Dose Regimen)[1] | Metformin | |
|---|---|---|---|
| | | Change[2] in AUC[3] | Change[2] in $C_{max}$ |
| **No dosing adjustments required for the following:** | | | |
| Glyburide (5 mg) | 850 mg | ↓9%[4] | ↓7%[4] |
| Furosemide (40 mg) | 850 mg | ↑15%[4] | ↑22%[4] |
| Nifedipine (10 mg) | 850 mg | ↑9% | ↑20% |
| Propranolol (40 mg) | 850 mg | ↓10% | ↓6% |
| Ibuprofen (400 mg) | 850 mg | ↑5%[4] | ↑7%[4] |
| **Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution** [see *Warnings and Precautions (5.10)* and *Drug Interactions (7.3)*]. | | | |
| Cimetidine (400 mg) | 850 mg | ↑40% | ↑60% |

1. All metformin and co-administered drugs were given as single doses.
2. Percent change (with/without co-administered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
3. AUC = AUC(INF).
4. Ratio of arithmetic means.

#### *Effects of Metformin on Other Drugs*

Table 7 shows the effect of metformin on other co-administered drugs.

**Table 7: Effect of Metformin on Co-administered Drug Systemic Exposure**

| Co-administered Drug (Dose Regimen)[1] | Metformin (Dose Regimen)[1] | Co-administered Drug | |
|---|---|---|---|
| | | Change[2] in AUC[3] | Change[2] in $C_{max}$ |
| **No dosing adjustments required for the following:** | | | |
| Glyburide (5 mg) | 850 mg | ↓22%[4] | ↓37%[4] |
| Furosemide (40 mg) | 850 mg | ↓12%[4] | ↓31%[4] |
| Nifedipine (10 mg) | 850 mg | ↑10%[5] | ↑8% |
| Propranolol (40 mg) | 850 mg | ↑1%[5] | ↑2% |
| Ibuprofen (400 mg) | 850 mg | ↓3%[6] | ↑1%[6] |
| **Co-administered Drug (Dose Regimen)[1]** | **Metformin (Dose Regimen)[1]** | **Co-administered Drug** | |
| | | **Change[2] in AUC[3]** | **Change[2] in $C_{max}$** |
| Cimetidine (400 mg) | 850 mg | ↓5%[5] | ↑1% |

1. All metformin and co-administered drugs were given as single doses.
2. Percent change (with/without co-administered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
3. AUC = AUC(INF) unless otherwise noted.
4. Ratio of arithmetic means, p-value of difference <0.05.
5. AUC(0-24 hr) reported.
6. Ratio of arithmetic means.

### *Effects of Other Drugs on Dapagliflozin*

Table 8 shows the effect of co-administered drugs on dapagliflozin. No dose adjustments are recommended for dapagliflozin.

**Table 8: Effects of Co-administered Drugs on Dapagliflozin Systemic Exposure**

| Co-administered Drug (Dose Regimen)[1] | Dapagliflozin (Dose Regimen)[1] | Dapagliflozin | |
|---|---|---|---|
| | | Change[2] in AUC[3] | Change[2] in $C_{max}$ |
| **No dosing adjustments required for the following:** | | | |
| **Oral Antidiabetic Agents** | | | |
| Metformin (1000 mg) | 20 mg | ↓1% | ↓7% |
| Pioglitazone (45 mg) | 50 mg | 0% | ↑9% |
| Sitagliptin (100 mg) | 20 mg | ↑8% | ↓4% |
| Glimepiride (4 mg) | 20 mg | ↓1% | ↑1% |
| Voglibose (0.2 mg three times daily) | 10 mg | ↑1% | ↑4% |

| | | | |
|---|---|---|---|
| **Cardiovascular Agents** | | | |
| Hydrochlorothiazide (25 mg) | 50 mg | ↑7% | ↓1% |
| Bumetanide (1 mg) | 10 mg once daily for 7 days | ↑5% | ↑8% |
| Valsartan (320 mg) | 20 mg | ↑2% | ↓12% |
| Simvastatin (40 mg) | 20 mg | ↓1% | ↓2% |
| **Anti-infective Agent** | | | |
| Rifampin (600 mg once daily for 6 days) | 10 mg | ↓22% | ↓7% |
| **Non-Steroidal Anti-inflammatory Agent** | | | |
| Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours) | 10 mg | ↑51% | ↑13% |

1. Single dose unless otherwise noted.

2. Percent change (with/without co-administered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

3. AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

### *Effects of Dapagliflozin on Other Drugs*

Table 9 shows the effect of dapagliflozin on other co-administered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the co-administered drugs.

**Table 9: Effects of Dapagliflozin on the Systemic Exposures of Co-administered Drugs**

| **Co-administered Drug (Dose Regimen)[1]** | **Dapagliflozin (Dose Regimen)[1]** | **Co-administered Drug** | |
|---|---|---|---|
| | | **Change[2] in AUC [3]** | **Change[2] in $C_{max}$** |
| **Co-administered Drug (Dose Regimen)[1]** | **Dapagliflozin (Dose Regimen)[1]** | **Co-administered Drug** | |
| | | **Change[2] in AUC [3]** | **Change[2] in $C_{max}$** |
| **No dosing adjustments required for the following:** | | | |
| **Oral Antidiabetic Agents** | | | |
| Metformin (1000 mg) | 20 mg | 0% | ↓5% |
| Pioglitazone (45 mg) | 50 mg | 0% | ↓7% |
| Sitagliptin (100 mg) | 20 mg | ↑1% | ↓11% |
| Glimepiride (4 mg) | 20 mg | ↑13% | ↑4% |
| **Cardiovascular Agents** | | | |

| | | | |
|---|---|---|---|
| Hydrochlorothiazide (25 mg) | 50 mg | ↓1% | ↓5% |
| Bumetanide (1 mg) | 10 mg once daily for 7 days | ↑13% | ↑13% |
| Valsartan (320 mg) | 20 mg | ↑5% | ↓6% |
| Simvastatin (40 mg) | 20 mg | ↑19% | ↓6% |
| Digoxin (0.25 mg) | 20 mg loading dose then 10 mg once daily for 7 days | 0% | ↓1% |
| Warfarin (25 mg)<br>S-warfarin<br>R-warfarin | 20 mg loading dose then 10 mg once daily for 7 days | <br>↑3%<br>↑6% | <br>↑7%<br>↑8% |

1. Single dose unless otherwise noted.
2. Percent change (with/without co-administered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.
3. AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

# 12 NONCLINICAL TOXICOLOGY

## 12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

*XIGDUO XR*

No animal studies have been conducted with XIGDUO XR to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and metformin individually.

*Dapagliflozin*

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-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 approximately 72 times (males) and 105 times (females) the clinical dose of 10 mg/day based on AUC exposure. In rats, the highest dose was approximately 131 times (males) and 186 times (females) the clinical dose of 10 mg per day based on AUC exposure.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than2100 times the clinical dose.

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708 times and 998 times the maximum recommended human doses in males and females, respectively.

*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 and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the maximum recommended human 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 dose based on body surface area comparisons.

## 13 CLINICAL STUDIES

There have been no clinical efficacy studies conducted with XIGDUO XR combination tablets to characterize its effect on HbA1c reduction. XIGDUO XR is considered to be bioequivalent to co-administered dapagliflozin and metformin hydrochloride extended-release (XR) tablets [see *Clinical Pharmacology (12.3)*]. Relative bioavailability studies between XIGDUO XR and co-administered dapagliflozin and metformin hydrochloride immediate-release (IR) tablets have not been conducted. The metformin hydrochloride XR tablets and metformin hydrochloride IR tablets have a similar extent of absorption (as measured by AUC), while peak plasma levels of XR tablets are approximately 20% lower than those of IR tablets at the same dose.

### 13.1 Glycemic Control

The coadministration of dapagliflozin and metformin XR tablets has been studied in treatment-naive patients inadequately controlled on diet and exercise alone. The coadministration of dapagliflozin and metformin IR or XR tablets has been studied in patients with type 2 diabetes mellitus inadequately controlled on metformin and compared with a sulfonylurea (glipizide) in combination with metformin. Treatment with dapagliflozin plus metformin at all doses produced clinically relevant and statistically significant improvements in HbA1c and fasting plasma glucose (FPG) compared to placebo in combination with metformin (initial or add-on therapy). HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI).

#### Initial Combination Therapy with Metformin Extended-Release

A total of 1236 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥7.5% and ≤12%) participated in 2 active-controlled studies of 24-week duration to initial therapy with dapagliflozin 5 mg or 10 mg in combination with metformin XR formulation.

In one study, 638 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: dapagliflozin 10 mg plus metformin XR (up to 2000 mg/day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 10 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 10 and Figure 2). Dapagliflozin 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was noninferior to metformin XR monotherapy in lowering HbA1c.

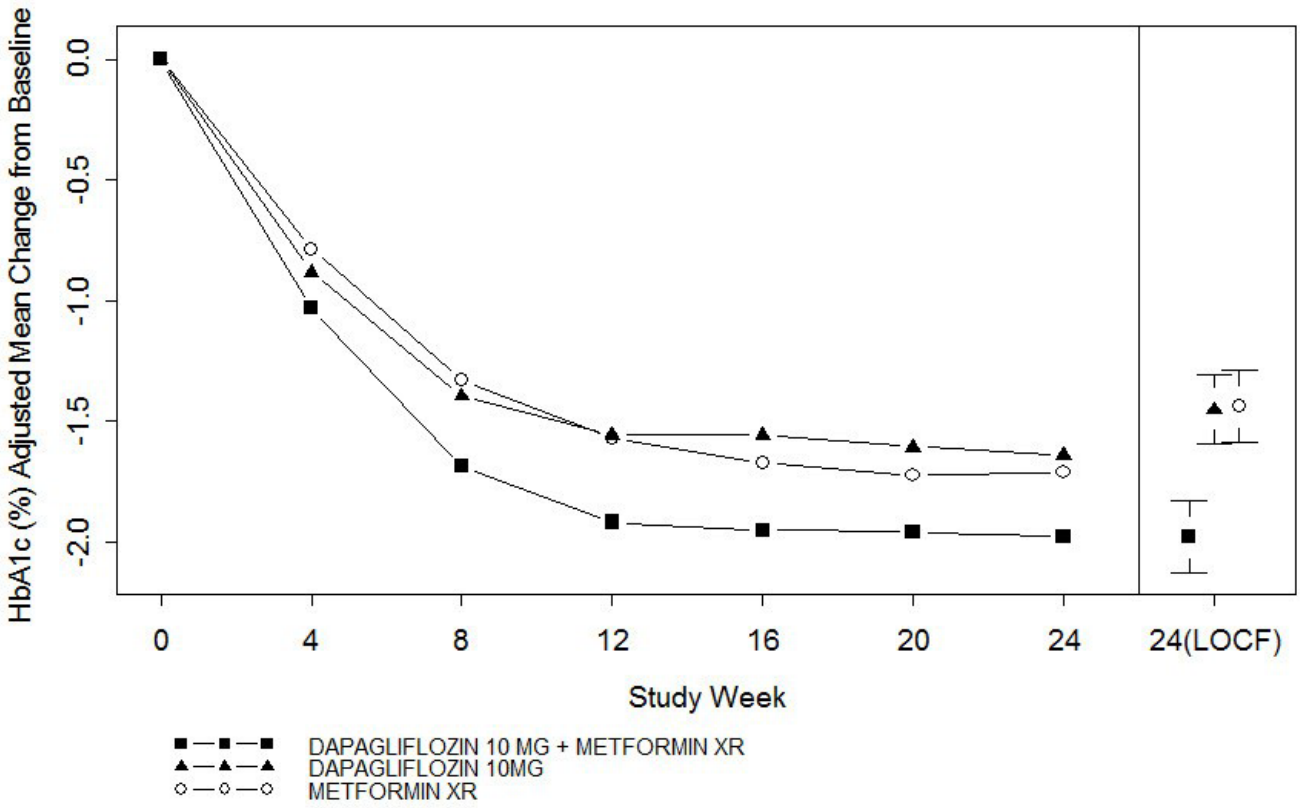
**Table 10 Results at Week 24 (LOCF[1]) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR**

| Efficacy Parameter | Dapagliflozin 10 mg + Metformin XR N=211[2] | Dapagliflozin 10 mg N=219[2] | Metformin XR N=208[2] |
|---|---|---|---|
| **HbA1c (%)** | | | |
| Baseline (mean) | 9.1 | 9.0 | 9.0 |
| Change from baseline (adjusted mean[3]) | −2.0 | −1.5 | −1.4 |
| Difference from dapagliflozin (adjusted mean[3]) (95% CI) | −0.5 [4] (−0.7, −0.3) | | |
| Difference from metformin XR (adjusted mean[3]) (95% CI) | −0.5 [4] (−0.8, −0.3) | 0.0 [5] (−0.2, 0.2) | |
| Percent of patients achieving HbA1c <7% adjusted for baseline | 46.6% | 31.7% | 35.2% |
| **FPG (mg/dL)** | | | |
| Baseline (mean) | 189.6 | 197.5 | 189.9 |
| Change from baseline (adjusted mean[3]) | −60.4 | −46.4 | −34.8 |
| Difference from dapagliflozin (adjusted mean[3]) (95% CI) | −13.9 [4] (−20.9, −7.0) | | |
| Difference from metformin XR (adjusted mean[3]) (95% CI) | −25.5 [4] (−32.6, −18.5) | −11.6 [6] (−18.6, −4.6) | |
| **Body Weight (kg)** | | | |
| Baseline (mean) | 88.6 | 88.5 | 87.2 |
| Change from baseline (adjusted mean[3]) | −3.3 | −2.7 | −1.4 |
| Difference from metformin XR (adjusted mean[3]) (95% CI) | −2.0 [4] (−2.6, −1.3) | −1.4 [4] (−2.0, −0.7) | |

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

2. All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
3. Least squares mean adjusted for baseline value.
4. p-value <0.0001.
5. Noninferior versus metformin XR.
6. p-value <0.05.

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




Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed the study with both baseline and Week 24 HbA1C values without rescue.
Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

In the second study, 603 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: dapagliflozin 5 mg plus metformin XR (up to 2000 mg/day), dapagliflozin 5 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 11).

**Table 11: Results at Week 24 (LOCF[1]) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR**

| Efficacy Parameter | Dapagliflozin 5 mg + Metformin XR N=194[2] | Dapagliflozin 5 mg N=203[2] | Metformin XR N=201[2] |
|---|---|---|---|
| **HbA1c (%)** | | | |
| Baseline (mean) | 9.2 | 9.1 | 9.1 |
| Change from baseline (adjusted mean[3]) | −2.1 | −1.2 | −1.4 |
| Difference from dapagliflozin (adjusted mean[3]) (95% CI) | −0.9 [4] (−1.1, −0.6) | | |
| Difference from metformin XR (adjusted mean[3]) (95% CI) | −0.7 [4] (−0.9, −0.5) | | |
| Percent of patients achieving HbA1c <7% adjusted for baseline | 52.4%[5] | 22.5% | 34.6% |
| **FPG (mg/dL)** | | | |
| Baseline (mean) | 193.4 | 190.8 | 196.7 |
| Change from baseline (adjusted mean[3]) | −61.0 | −42.0 | −33.6 |
| Difference from dapagliflozin (adjusted mean[3]) (95% CI) | −19.1 [4] (−26.7, −11.4) | | |
| Difference from metformin XR (adjusted mean[3]) (95% CI) | −27.5 [4] (−35.1, −19.8) | | |
| **Body Weight (kg)** | | | |
| Baseline (mean) | 84.2 | 86.2 | 85.8 |
| Change from baseline (adjusted mean[3]) | −2.7 | −2.6 | −1.3 |
| Difference from metformin XR (adjusted mean[3]) (95% CI) | −1.4 [4] (−2.0, −0.7) | | |

1. LOCF: last observation (prior to rescue for rescued patients) carried forward.
2. All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
3. Least squares mean adjusted for baseline value.
4. p-value <0.0001.
5. p-value <0.05.

## Add-On to Metformin Immediate-Release

A total of 546 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study 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 5 mg, dapagliflozin 10 mg, or placebo in addition to their current dose of metformin.

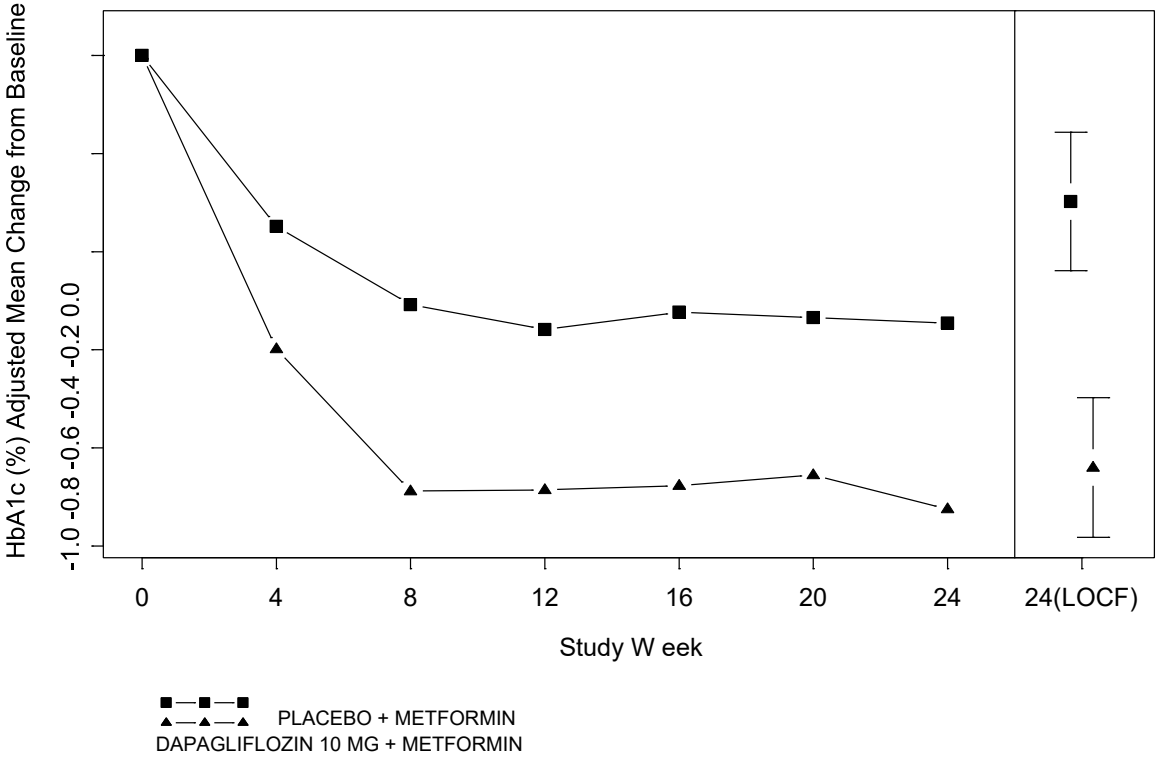
As add-on treatment to metformin, dapagliflozin 10 mg provided statistically significant improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at Week 24 (see Table 12 and Figure 3). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were −4.5 mmHg and −5.3 mmHg with dapagliflozin 5 mg and 10 mg plus metformin, respectively.

**Table 12: Results of a 24-Week (LOCF[1]) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin**

| Efficacy Parameter | Dapagliflozin 10 mg + Metformin N=1352 | Dapagliflozin 5 mg + Metformin N=1372 | Placebo + Metformin N=1372 |
|---|---|---|---|
| **HbA1c (%)** | | | |
| Baseline (mean) | 7.9 | 8.2 | 8.1 |
| Change from baseline (adjusted mean3) | −0.8 | −0.7 | −0.3 |
| Difference from placebo (adjusted mean 3) (95% CI) | −0.54 (−0.7, −0.3) | −0.44 (−0.6, −0.2) | |
| Percent of patients achieving HbA1c <7% adjusted for baseline | 40.6%5 | 37.5%5 | 25.9% |
| **FPG (mg/dL)** | | | |
| Baseline (mean) | 156.0 | 169.2 | 165.6 |
| Change from baseline at Week 24 (adjusted mean3) | −23.5 | −21.5 | −6.0 |
| Difference from placebo (adjusted mean 3) (95% CI) | −17.54 (−25.0, −10.0) | −15.54 (−22.9, −8.1) | |
| Change from baseline at Week 1 (adjusted mean3) | −16.54 (N=115) | −12.04 (N=121) | 1.2 (N=126) |
| **Body Weight (kg)** | | | |
| Baseline (mean) | 86.3 | 84.7 | 87.7 |
| Change from baseline (adjusted mean 3) | −2.9 | −3.0 | −0.9 |
| Difference from placebo (adjusted mean 3) (95% CI) | −2.04 (−2.6, −1.3) | −2.24 (−2.8, −1.5) | |

1. LOCF: last observation (prior to rescue for rescued patients) carried forward.
2. All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
3. Least squares mean adjusted for baseline value.
4. p-value <0.00001 versus placebo + metformin.
5. p-value <0.05 versus placebo + metformin.

**Figure 3: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Placebo-Controlled Study of Dapagliflozin in Combination with Metformin**




Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed Short-Term Period with both baseline and Week 24 HbA1C values without rescue. Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

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

A total of 816 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, glipizide-controlled, noninferiority study to evaluate dapagliflozin as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg/day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 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.

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 treatment led to a similar mean reduction in HbA1c from baseline at Week 52, compared with glipizide, thus demonstrating noninferiority (see Table 13). Dapagliflozin treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 compared with a mean increase in body weight in the glipizide group. Statistically significant ($p<0.0001$) mean change from baseline in systolic blood pressure relative to glipizide plus metformin was −5.0 mmHg with dapagliflozin plus metformin.

**Table 13: Results at Week 52 (LOCF[1]) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-On to Metformin**

| Efficacy Parameter | Dapagliflozin + Metformin N=400[2] | Glipizide + Metformin N=401[2] |
|---|---|---|
| **HbA1c (%)** | | |
| Baseline (mean) | 7.7 | 7.7 |
| Change from baseline (adjusted mean[3]) | −0.5 | −0.5 |
| Difference from glipizide + metformin (adjusted mean[3]) (95% CI) | 0.0[4] (−0.1, 0.1) | |
| **Body Weight (kg)** | | |
| Baseline (mean) | 88.4 | 87.6 |
| Change from baseline (adjusted mean[3]) | −3.2 | 1.4 |
| Difference from glipizide + metformin (adjusted mean[3]) (95% CI) | −4.7 [5] (−5.1, −4.2) | |

1. LOCF: last observation carried forward.
2. Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement.
3. Least squares mean adjusted for baseline value.
4. Noninferior to glipizide + metformin.
5. p-value <0.0001.

## Use in Patients with Type 2 Diabetes Mellitus 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 mellitus 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 14).

**Table 14: Results at Week 24 of Placebo-Controlled Study for Dapagliflozin in Patients with Type 2 Diabetes Mellitus 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

## 13.2 Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Dapagliflozin Effect on Cardiovascular Events (DECLARE, NCT01730534) was an international, multicenter, randomized, double-blind, placebo-controlled, clinical study conducted to determine the effect of dapagliflozin 10 mg relative to placebo on cardiovascular (CV) outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CV disease or two or more additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension, or current tobacco use). Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

Of 17160 randomized patients, 6974 (40.6%) had established CV disease and 10186 (59.4%) did not have established CV disease. A total of 8582 patients were randomized to dapagliflozin 10 mg, 8578 to placebo, and patients were followed for a median of 4.2 years. Approximately 80% of the trial population was White, 4% Black or African American, and 13% Asian. The mean age was 64 years, and approximately 63% were male. Mean duration of diabetes was 11.9 years and 22.4% of patients had diabetes for less than 5 years. Mean eGFR was 85.2 mL/min/1.73 m2. At baseline, 23.5% of patients had microalbuminuria (UACR ≥30 to ≤300 mg/g) and 6.8% had macroalbuminuria (UACR >300 mg/g). Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m2. At baseline, 10% of patients had a history of heart failure.

Most patients (98.1%) used one or more antihyperglycemic medications at baseline. 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 receptor agonist.

Approximately 81.3% of patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics, and 10.5% with loop diuretics.

A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio (HR) of the composite of CV death, myocardial infarction (MI), or ischemic stroke (MACE) and if non-inferiority was demonstrated, to test for superiority on the two primary endpoints: 1) the composite of hospitalization for heart failure or CV death, and 2) MACE. The incidence rate of MACE was similar in both treatment arms: 2.30 MACE events per 100 patient-years on dapagliflozin vs 2.46 MACE events per 100 patient-years on placebo. The estimated hazard ratio of MACE associated with dapagliflozin relative to placebo was 0.93 with a 95% CI of (0.84, 1.03). The upper bound of this confidence interval, 1.03, excluded the prespecified non-inferiority margin of 1.3.
Dapagliflozin 10 mg was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]).
The treatment effect was due to a significant reduction in the risk of hospitalization for heart failure in subjects randomized to dapagliflozin 10 mg (HR 0.73 [95% CI 0.61, 0.88]), with no change in the risk of CV death (Table 15 and Figures 4 and 5).

## Table 15: Treatment Effects for the Primary Endpoints* and their Components* in the DECLARE Study

| | Patients with events n(%) | | |
|---|---|---|---|
| **Efficacy Variable (time to first occurrence)** | **Dapagliflozin 10 mg N=8582** | **Placebo N=8578** | **Hazard Ratio (95% CI)** |
| **Primary Endpoints** | | | |
| **Composite of Hospitalization for Heart Failure, CV Death**[†] | 417 (4.9) | 496 (5.8) | 0.83 (0.73, 0.95) |
| **Composite Endpoint of CV Death, MI, Ischemic Stroke** | 756 (8.8) | 803 (9.4) | 0.93 (0.84, 1.03) |
| Components of the composite endpoints[‡] | | | |
| Hospitalization for Heart Failure | 212 (2.5) | 286 (3.3) | 0.73 (0.61, 0.88) |
| CV Death | 245 (2.9) | 249 (2.9) | 0.98 (0.82, 1.17) |
| Myocardial Infarction | 393 (4.6) | 441 (5.1) | 0.89 (0.77, 1.01) |
| Ischemic Stroke | 235 (2.7) | 231 (2.7) | 1.01 (0.84, 1.21) |

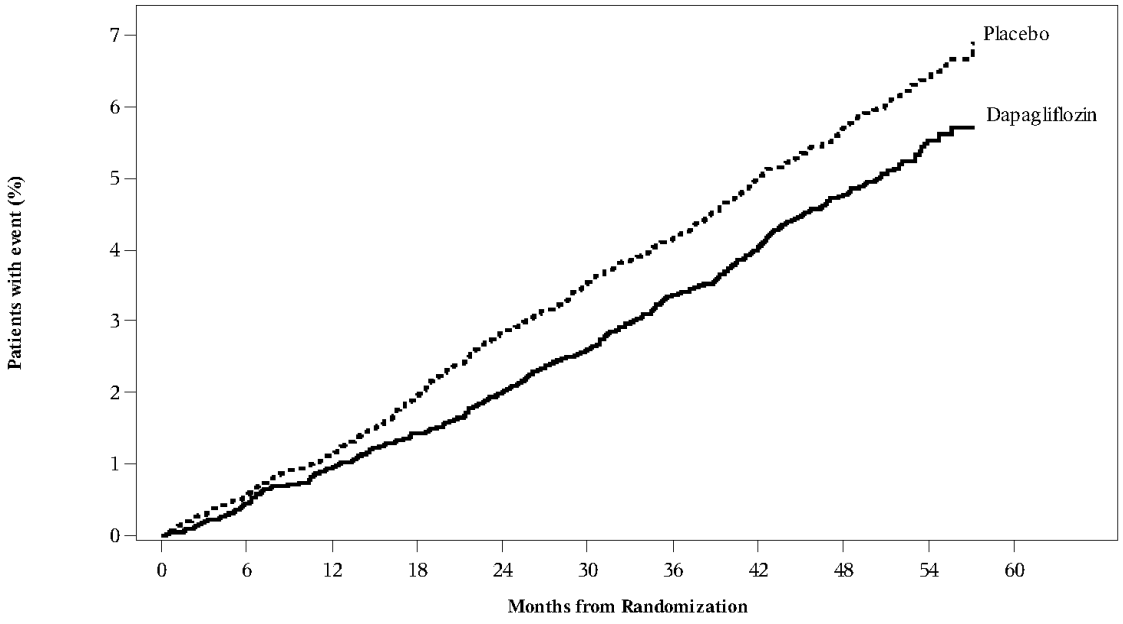
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction, eGFR=estimated glomerular filtration rate, ESRD=End-stage renal disease

* Full analysis set.

† p-value =0.005 versus placebo.

‡ total number of events presented for each component of the composite endpoints.

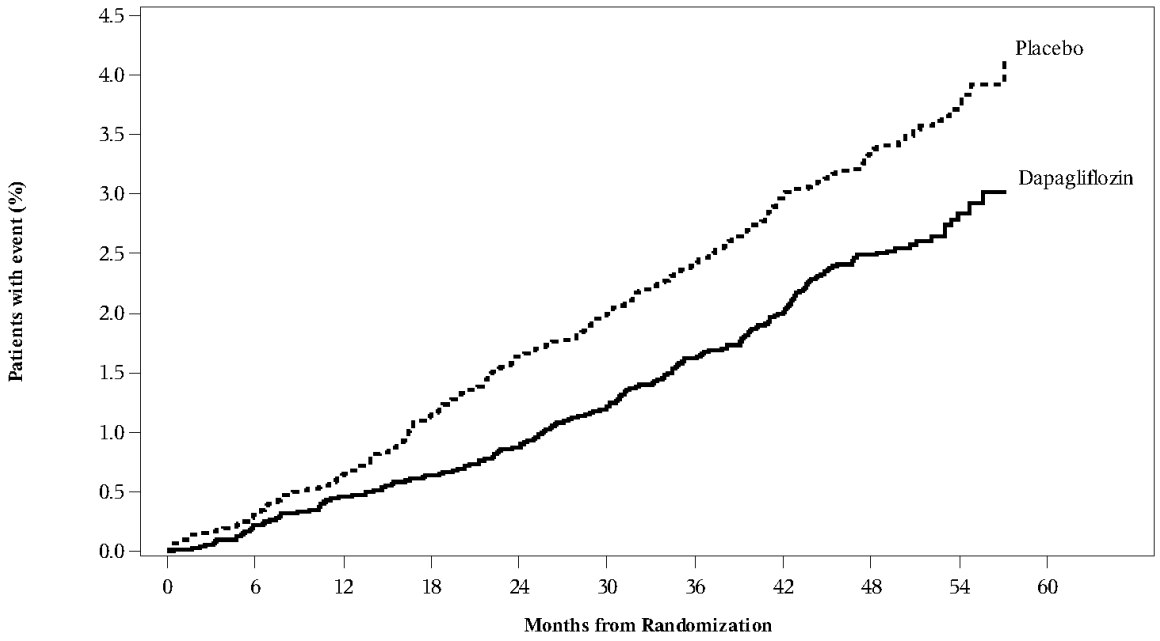
**Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study**




**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 |

**Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study**




**Patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin: | 8582 | 8509 | 8403 | 8315 | 8218 | 8101 | 7965 | 7489 | 5439 | 1626 |
| Placebo: | 8578 | 8482 | 8380 | 8256 | 8121 | 7998 | 7874 | 7360 | 5358 | 1572 |

# 14 HOW SUPPLIED/STORAGE AND HANDLING

## How Supplied

XIGDUO™ XR (dapagliflozin and metformin hydrochloride extended-release) tablets have markings on one side, are plain on the reverse side, and are available in the strengths and packages listed in Table 16.

**Table 16: XIGDUO XR Tablet Presentations**

| Tablet Strength | Film-Coated Tablet Color/Shape | Tablet Markings | Pack Size |
|---|---|---|---|
| **5/500 mg** | orange, biconvex, capsule-shaped | "1070" and "5/500" debossed on one side and plain on the reverse side. | Alu/Alu blister 7, 14, 28, 56 tablets |
| **5/1000 mg** | pink to dark pink, biconvex, oval-shaped | "1071" and "5/1000" debossed on one side and plain on the reverse side. | Alu/Alu blister 7, 14, 28, 56 tablets |
| **10/500 mg** | pink, biconvex, capsule-shaped | "1072" and "10/500" debossed on one side and plain on the reverse side. | Alu/Alu blister 7, 14, 28, 56 tablets |
| **10/1000 mg** | yellow to dark yellow, biconvex, oval-shaped | "1073" and "10/1000" debossed on one side and plain on the reverse side | Alu/Alu blister 7, 14, 28, 56 tablets |

**Storage and Handling**

Store below 30°C

**Manufacturer:** Bristol-Myers Squibb Manufacturing Company, State Road#3, Km 77.5 Humacao, Puerto Rico 00791

**License Holder and importer:** AstraZeneca (Israel) Ltd., 1 Atirei Yeda St., Kfar Saba 4464301

Revised on Jan 2023